

**THE EFFECT OF OESTROGEN TREATMENT ON SLEEP, MOOD, ANXIETY
AND HOT FLUSHES IN PERIMENOPAUSAL WOMEN.**

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ABSTRACT

The menopause is associated with many symptoms, but surveys have shown that hot flushes, insomnia, and psychological symptoms are especially common in the perimenopausal years. Menopausal symptoms are often treated by hormone replacement therapy because the menopause is associated with changing hormone levels, but the value of treatment has not been conclusively proven.

The aim of my study was to determine the effect of oestrogen treatment on sleep, mood, anxiety, and hot flushes in perimenopausal women. Patients in the study were women aged 45-55, with at least three months amenorrhoea and symptoms of insomnia, depression, anxiety, and hot flushes. The study was double blind and controlled, with half of the patients receiving six weeks placebo followed by eight weeks piperazine oestrone sulphate 3 mg/day, and half remaining on placebo throughout the study. Sleep was recorded electrophysiologically on one night per week, the first two nights being for adaptation purposes only, the next four in the baseline placebo period, the next four in the first treatment month, and the remaining four in the second treatment month. Patients rated their sleep quality, mood, anxiety levels, and hot flush severity daily using visual analogue scales, and recorded their daily hot flush count. Hamilton observer rating scales of depression and anxiety were completed at intervals during the study.

There were 17 patients in each group, and the two groups were similar in terms of age and duration of amenorrhoea. Electrophysiological sleep recording showed that during the first month of active treatment, the amount of wakefulness interrupting periods of sleep decreased more in the oestrone group than the placebo group. In the second treatment month, the oestrone group showed a further decrease in the amount of intervening wakefulness, a decrease in the frequency of waking, and an increase in their amount of REM sleep, all of which were significant when compared with the changes shown by the placebo group. The less sensitive visual analogue scales failed to differentiate between the groups. Mood and anxiety improved, and the number and severity of hot flushes decreased to a similar extent in the two groups.

Six patients in each group attended on two extra nights, when blood samples were taken at 20 min intervals while recording sleep to investigate their nocturnal plasma hormone levels. In all cases, plasma oestrone and oestradiol concentrations fluctuated rapidly and widely, but the mean levels of both hormones were low on placebo. The four patients studied after four weeks of oestrogen treatment showed an increase in their mean oestrone levels, but only two had higher mean oestradiol levels. Prolactin secretion increased after sleep onset in all cases, and oestrogen treatment had no consistent effect on prolactin secretion. Free and total plasma tryptophan levels were measured in three patients on placebo, and in each case a highly significant correlation was found between total plasma oestrogen concentration and both concentration and % free plasma tryptophan.

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I declare that this thesis has been composed by myself.

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INTRODUCTION

The menopause is defined as the time of the last menstrual period, but in current usage it is synonymous with the climacterium, the time when reproductive function declines and is lost. It is a normal, physiological event of middle age for women, yet for many it is a source of anxiety, as they fear it will bring physical or mental upset, or that they will age rapidly after it. Most women experience some symptoms around the time of the menopause, and even minor symptoms such as hot flushes can be tiresome and embarrassing, so it is not surprising that many women request hormone replacement therapy, in the hope that it will not only relieve their symptoms but also prolong their youth and attractiveness.

Oestrogen treatment is not without risk, as Coope et al (1975) have shown that it can affect blood clotting mechanisms in postmenopausal women, and may increase the risk of thromboembolic disease, and Smith et al (1975) and Ziel and Finkle (1975) have reported that it may increase the risk of endometrial carcinoma, so this treatment should not be used indiscriminately. We believe that oestrogen will relieve atrophic vaginitis and osteoporosis, but other than this little is known about the effect of oestrogens on the symptoms of the menopause. Indeed, little is known about the symptoms of the menopause, and perusal of the literature will show that almost every symptom, physical or mental, which can be experienced by a middle aged woman has at some time been attributed to the menopause.

HISTORY

The view that the female reproductive organs are associated with mental disorder dates back to the second century A.D., when the Cappadocian physician, Aretaeus, claimed that hysteria was due to wandering of the womb in the body. The menopause was known in those days, and had been described by Soranus in his textbook of gynaecology written around 100 AD, but was not considered to be a cause of either physical or mental ill health. Of course, life expectancy at that time was short, and since few women can have lived to experience the menopause, it is unlikely to have been a major problem.

The first known reference in the medical literature to a menopausal complaint is the report by Willis in 1684 of a woman of 50 who developed 'convulsions in the stomach' six months after the menopause. Little interest was taken in the menopause until the 19th century when Tilt (1858) published a treatise on the change of life in which he reported that 90% of women experienced 'nervous irritability' during the menopause. Tilt also reported that 51% experienced hot flushes and 41% headaches, and he continued to list 135 less common symptoms, including such unlikely ones as blind piles, boils in the seat, haemoptysis, aortic pulsation, haemorrhage from the ears, and temporary deafness. Hegar (1878) added hyperaesthesia, prickling and burning sensations, uncertain gait, muscular weakness, insomnia, migraine and hallucinations, and Börner (1886) added personality change and quick temper to the growing list of

menopausal symptoms. Later authors added to this growing catalogue of psychological symptoms. Eymer (1927) added scandal-mongering, untruthfulness, and forgetfulness and Pappenheim (1930) added explosive affect, nightmares, hypochondria, fear of madness, pyromania, and kleptomania. These authors all gave anecdotal accounts of their experience without attempting to separate cause and effect, and in 1933 a survey was commissioned by the Medical Women's Federation to attempt to determine which symptoms are commonly associated with the menopause. This showed that hot flushes and nervous instability are indeed common complaints after the menopause, but neither this nor subsequent studies have demonstrated the existence of a menopausal syndrome, nor shown which symptoms are caused by the menopause.

The view that the menopause might be related to mental illness was first expressed by Brière de Boismont (1842) when he observed that the menopause was often followed by melancholia. This relationship was investigated by Merson (1876), who found a high percentage of new admissions to a psychiatric hospital showed a temporal relationship to the menopause, since in 69 cases the illness developed just before, and 147 cases just after, complete cessation of menstruation. He described a variety of syndromes, including simple depression with nervous irritability, more severe depression with intellectual disturbance, and depression with hallucinations, depressive delusions, and delusions of suspicion or persecution. Merson did not

blame the menopause as the sole cause of psychotic illness, but reported that many women had additional problems such as bereavement, physical illness, unhappy marriages, or financial problems which had contributed to their illness. Other authors held conflicting views on the relationship between the menopause and mental illness. Tilt (1858) considered that the menopause might cure insanity, while Maudsley (1867) stated that it caused a specific psychosis and Buckham (1888) and Currier (1898) denied that it had any role at all in the causation of mental illness. The most widely held view, however, was that expressed by von Krafft-Ebing (1877), that the menopause could cause a wide variety of minor psychiatric symptoms, and was at times a contributory cause of psychosis. He considered that sexual delusions and ideas of influence were typical of psychotic illnesses around the time of the menopause.

The relationship between involutional melancholia and the menopause has also caused controversy. Involutional melancholia is a depressive illness occurring in the involutional period in both sexes, usually in people with a rigid, introverted, and obsessional premorbid personality, and its clinical features include marked anxiety and agitation, hypochondriasis with bizarre somatic delusions, paranoid ideas, nihilistic delusions, and feelings of unreality. In 1896 Kraepelin classified it as a discrete category of functional psychosis because depression was unduly common in middle age, had a prolonged course, and frequently terminated in dementia. He was criticised by

Dreyfus (1907) who re-examined Kraepelin's material and disagreed with this classification, and in 1913 Kraepelin reversed his view that involutional melancholia was a discrete entity, partly because of this criticism and partly because he had realised that the increase in depression in middle age is only the start of a progressive increase in depression which lasted into senescence, and which could be caused by dementia. Since then, opinions have been divided about the place of involutional melancholia. Palmer and Sherman (1938) and Malamud et al (1949) compared the symptoms of a group of patients diagnosed as involutional melancholia with typical symptoms of manic-depressive illness in a younger population, and concluded that involutional melancholia does exist as a discrete entity. Since it occurs in middle age, it was considered likely that involutional melancholia was related to the menopause in women. Farrar and Franks (1931) found that the menopause and the onset of psychosis occurred within one year of each other in 60% of their cases, and Hemphill and Reiss (1940) even published four endocrine patterns in involutional melancholia. However, more recent research has shown that it is unlikely to be due to hormonal factors, as Nedbailova (1962) showed that oestrogen secretion was normal in 14 out of 18 women with involutional melancholia, and Nikula-Baumann (1971) could find no difference in either oestrogen or gonadotrophin levels between cases and controls. Recent research has shown that involutional melancholia is now rarely diagnosed. Tait et al (1957)

found no evidence of the typical symptoms of involutional melancholia in 29 depressives admitted to hospital for the first time between the ages of 40 and 55, and Rosenthal (1968) also noted the rarity of this syndrome and suggested that it may be due to early and effective treatment with antidepressants. Involutional melancholia is not now considered to be a specific illness, but merely to be a depressive psychosis such as occurs at all stages of life, coloured by the life events of middle age.

The theory that menopausal symptoms are due to ovarian deficiency dates back to the nineteenth century, when oophorectomy was used as a treatment for neurosis and dysmenorrhoea. Hegar (1878) reported that oophorectomy is identical to the menopause and produces the same symptoms, and when treatment by organotherapy was introduced by Brown-Séquard in 1889 it seemed logical to treat menopausal symptoms with ovarian extract. Brown-Séquard (1889) claimed that injections of testicular extract had rejuvenated him and in a later paper (1893) claimed that ovarian extract had a similar effect on women, and that his colleague, Augusta Brown, had treated 60 old women with good effect. This treatment was heralded by the lay press as the 'elixir of youth', a title which is used at times for hormone replacement therapy in the lay press to the present day. However, in the medical world this treatment was less popular, with some physicians claiming good results and others no effect at all. This may have been due to the varying potency of the treatments used,

since some used minced fresh ovaries, some dessicated ovarian tablets, and some extracts in water and in glycerine, and it was not until 1912 that it was discovered that the active substance could be extracted using a lipid solvent. This purified extract was marketed as theelin, and was widely used in the 1930's. In a clinical trial, Pratt and Thomas (1937) failed to show that this product was more effective than the placebo in treating menopausal symptoms but Hawkinson (1938) reported excellent results in treating 1000 patients, and its use continued. Theelin was also tried as a treatment for involutional melancholia in women. Werner et al (1934; 1936) and Suckle and Coatesville (1937) found that theelin was an effective treatment, but their study designs were poor, and their results inconclusive, and Bowman and Bender (1932) and Shube et al (1937) found that it had little effect. Since the results of treatment of involutional melancholia on the whole were poor, oestrogen treatment was not widely used, and with the discovery of active antidepressant drugs was superseded altogether. However, the use of oestrogens in the treatment of menopausal symptoms continues, and with the increase in knowledge of endocrinology it is now possible to give purified or synthetic hormones orally as well as by injection. This treatment is popular, but is not yet completely evaluated.

Not all workers agree that menopausal symptoms are due to hormonal changes. In the early twentieth century interest was focussed on the psychodynamic schools of

psychiatry, and in particular in the psychoanalytic school of thought. This was originated by Freud, who considered that neurotic symptoms were derived from sexual experiences in childhood. Freud himself had little interest in the menopause, but later analytic writers regard it as a pathogenic factor because of its symbolic significance. According to psychoanalytic theory, little girls experience a penis envy in childhood which is resolved by identification with their mothers and the discovery that they are able to bear children. The menopause means the end of this biological function, and Deutsch (1945) described it as a partial death followed by a struggle against decline, Benedek (1950) as a time of desexualisation, and Prados (1967) as a threatening, unavoidable loss, and they regard conflicts about approaching infertility as a cause of many of the menopausal symptoms. They recommend psychoanalytic psychotherapy as treatment for menopausal symptoms, to enable the woman to adjust to the approaching loss, though Benedek also recommends the use of hormone treatment since she considers that falling production of ovarian hormones decreases the ego's capacity to love.

Other workers have considered menopausal psychological symptoms to be due to a reaction to the social events of middle age. Greenhill (1946) suggested that they may be due to marital problems, and Deykin et al (1966) described the 'empty nest syndrome' of depression in the mother when the children have left home.

Considering the vast literature which now exists on the menopause, the symptoms associated with it, and their treatment, it is not surprising that so much confusion exists in this field. Uncertainty about the time course and symptoms has led to clinical trials that have produced conflicting results by studying different symptoms and populations, and this has added to the confusion. Even the rationale for hormone replacement therapy is now in doubt, since advances in physiology have shown that the menopause is far from a simple ovarian failure, but causes complex metabolic changes.

PHYSIOLOGY

Throughout reproductive life women experience the monthly changes of the menstrual cycle unless they become pregnant. At the start of the cycle, gonadotrophins stimulate the development of a follicle in the ovary, and an increase in the secretion of ovarian oestrogens. At midcycle there is a peak in gonadotrophin secretion which causes ovulation, and the ovarian follicle develops into the corpus luteum. In the second part of the cycle, the secretion of oestrogens increases, and progesterone too is secreted by the ovary. These hormonal changes of the menstrual cycle are complex, as can be seen from Fig. 1, and they are controlled by a feedback loop involving the hypothalamus, pituitary, and the ovaries. The polypeptide luteinising hormone releasing hormone (LHRH) is produced by the hypothalamus and passes via a portal blood system to the pituitary gland, where it promotes the release of the gonadotrophins luteinising hormone (LH) and follicle stimulating hormone (FSH). These stimulate the production of oestrogens, and in the second part of the cycle progesterone, by the ovary, and after release into the bloodstream the oestrogens have a negative feedback effect on the hypothalamus and inhibit the release of LHRH.

There are three main oestrogens, oestradiol, oestrone, and oestriol. The most potent is oestradiol, which is secreted by the ovary in premenopausal women, and its plasma level varies during the menstrual cycle from 128 pmol/l (35 pg/ml) to 1840 pmol/l (500 pg/ml) (Judd, 1976).

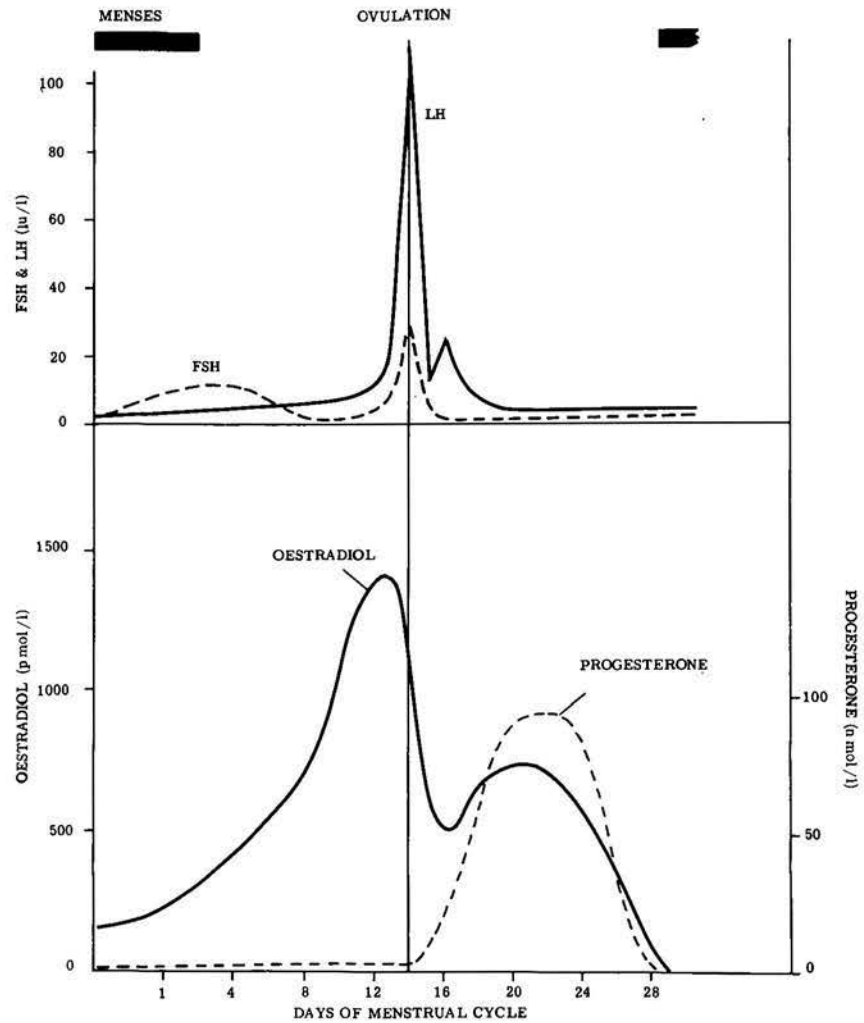


FIG. 1: Schematic representation of the changes in serum LH, FSH, progesterone, and oestradiol during the normal menstrual cycle in women.

Oestradiol is readily oxidised by the liver to oestrone, but this change is reversible and the conversion of oestrone to oestradiol may be the main source of circulating oestradiol after the menopause. During the menstrual cycle the level of oestrone is lower than that of oestradiol, ranging from 110 pmol/l (30 pg/ml) to 740 pmol/l (200 pg/ml) (Judd, 1976). The source of the circulating oestrone is complex in premenopausal women, as it comes partly from the ovary, partly from the adrenal, and partly from the conversion of oestradiol and androstenedione. Oestriol is the least potent of the three oestrogens, and is a peripheral metabolite produced by the hydration of oestrone, and it is present only in small quantities in the blood.

Treloar et al (1967) observed that with increasing age, the length of the menstrual cycle shortens, and as the menopause approaches it becomes irregular before menstruation finally ceases. The cessation of menstruation is a clearly defined event, but the changes leading up to it take place over a number of years. Gonadotrophin levels rise as the ovary becomes resistant to gonadotrophic stimulation, and finally follicular development and ovulation cease, causing a fall in the levels of the oestrogens and progesterone and cessation of menstruation. The high level of gonadotrophins can be reduced by administration of oestrogen, so the feedback mechanism must still be working at the level of the hypothalamus, but it is not possible to stimulate the ovary to produce oestrogen by the administration of gonadotrophins after the menopause.

The cause of this ovarian failure is unknown. It was believed to be due to follicular exhaustion of the ovary, but Block (1952) found that there were still a significant number of primordial follicles in the ovary at the time of the menopause, and Costoff and Mahesh (1975) reported that these follicles and ova appeared normal on electron microscopy. Why these follicles no longer respond to gonadotrophic stimulation after the menopause remains a mystery.

The menopause may also occur as a result of surgery, as both a hysterectomy and a bilateral oophorectomy result in the cessation of menstruation. Oophorectomy leads to hormonal changes similar to those of the physiological menopause, but if the ovaries are preserved intact at hysterectomy the hormone changes may not take place till the time when the menopause would have occurred spontaneously.

The most intensively studied hormone change associated with the menopause is the fall in oestrogen levels. Oestrogen levels were first estimated by vaginal cytology, since oestrogen deficiency is known to be associated with vaginal atrophy. In this method, a vaginal smear is examined and the proportions of superficial, intermediate, and parabasal cells determined. Oestrogen deficiency is associated with a decrease in the number of superficial cells and an increase in the number of parabasal cells. Randall et al (1957) carried out vaginal smears on 1768 postmenopausal women and found that although 40% showed evidence of oestrogen deficiency within 5 years of the

menopause, a further 40% did not show evidence of oestrogen deficiency after the age of 60, and Chapman et al (1976) observed atrophic smears in women who were still menstruating. This method of estimating oestrogenic activity is crude and inaccurate, and has been criticised by Masukawa (1960) on the grounds that the results are distorted by many factors such as bleeding, infection, prolapse, and the administration of other hormones, especially progesterone, and of drugs such as digitalis. It was shown by Larrison-Cohn et al (1977) that there was no correlation between vaginal epithelium appearances and plasma oestrogen levels, and although Coope et al (1975) found that the appearance of the vaginal smear was not related to the clinical state, and was of little value in judging treatment outcome, vaginal cytology continues to be used in some cases in controlling oestrogen treatment.

More recently methods have been devised for assaying oestrogens and gonadotrophins in urine and plasma by radio-immunoassay, and using these methods the hormonal changes of the peri- and postmenopausal periods have been investigated. Adamopoulos et al (1971) carried out serial assays of urinary FSH, LH, oestrogen, and pregnanediol in 12 women approaching the menopause. In the premenopausal phase, their FSH increased 3 times, and LH increased 7 times above the normal levels of premenopausal women, while their oestrogen and pregnanediol levels were lower than those of young women, and only 3 of the 12 cases showed hormone changes suggesting that ovulation had taken place. In

some cases, high LH levels coexisted with high levels of oestrogen, suggesting a disturbance in the feed-back mechanism.

Sherman et al (1976) studied plasma hormone levels in the perimenopausal period. In regularly menstruating perimenopausal women, they found elevated FSH levels and low oestradiol levels throughout the cycle, with a decrease in the interval between menstruation and the midcycle gonadotrophin peak. They studied two women over a two year period during the menopausal transition and observed cycles of varying length. In some cycles, they showed the hormonal changes associated with follicular maturation and corpus luteum functioning in the presence of high LH and FSH levels, with normal progesterone but decreased oestradiol levels. Later, as the menopause approached, both oestradiol and progesterone levels were low and anovulatory bleeding occurred as the oestradiol levels fell without any changes in progesterone having occurred.

Many workers have studied the plasma hormone levels of postmenopausal women, and since menopausal symptoms were believed to be due to oestrogen deficiency, oestrogen levels have been studied more than those of other hormones. Table 1 shows the mean plasma oestrone and oestradiol levels reported by various authors, and it can be seen from this that their results vary from very low levels to levels which might be expected during the menstrual cycle. Campbell (1976_a) and Hutton et al (1978) reported oestrone and oestradiol levels similar to those of the early

TABLE 1: Mean Plasma Oestrone and Oestradiol Levels in Postmenopausal Women - Review of the Literature

Authors	Mean Oestrone (pmol/l)	Mean Oestradiol (pmol/l)	Age Range
Baird and Guevara (1969)	263	48	70-89
Korenman et al (1969)	-	54	
Tulchinsky and Korenman(1970)	148	-	48-60
Longcope (1971)	92	24	74-89
Rader et al (1973)	152	48	31-82
Abraham and Maroulis (1975)	222	48	
Campbell (1976a)	168	137	
Chakravarti et al (1976)	89	52	49-91
Greenblatt et al (1976)	-	69	58-76
Vermeulen (1976)	181	74	52-65
Hutton et al (1978)	198	126	42-56
Lind et al (1978)	98	85	

proliferative phase of the menstrual cycle, while all of the other authors reported much lower oestradiol levels, and Longcope (1971), Chakravarti et al (1976), and Lind et al (1978) also found much lower oestrone levels. Before the menopause, oestradiol is the main oestrogen, and the oestrone:oestradiol ratio is less than one, but after the menopause the proportions of the two oestrogens change. All of the studies summarised in Table 1 have shown the oestrone:oestradiol ratio to be greater than 1, the lowest value being that of Lind et al (1978), who found a ratio of 1.2:1 and the highest value being 5.5:1, reported by

Vermeulen (1976). There are many possible causes for these different results. There may be differences in the sensitivity of the assay methods in different laboratories, and it can be seen from Table 1 that the various authors have studied different age groups, which may also have influenced the result.

Chakravarti et al (1976) have shown that oestrogen levels may change with time after the menopause. They studied the plasma hormone profiles of 60 postmenopausal women, taking two blood samples from each and assaying the plasma for oestrone, oestradiol, androstenedione, testosterone, FSH and LH. They presented their results as % of the hormone levels expected in the first 10 days of the menstrual cycle, and found that within one year of the menopause the mean oestrone, oestradiol, and androstenedione levels had fallen to 20% of these levels, while the concentration of FSH had increased by a factor of 13.4 and of LH by a factor of 3.0. Concentrations of the gonadotrophins reached a peak between two and three years after the menopause, when FSH was increased 18.4 times, and LH 3.4 times above the levels found in the early proliferative phase of the menstrual cycle, but over the next three decades their levels gradually fell to half the maximum value. Oestrone levels continued to fall after the menopause, but oestradiol levels began to rise again 10 years after the menopause, reaching in a few cases the lower normal levels of the menstrual cycle. They also noted a gradual fall in testosterone levels, contrary to the

findings of Greenblatt et al (1976), who reported that testosterone levels rose in women after the menopause.

Campbell (1976a) studied oestrone, oestradiol, and oestriol levels at 2-hourly intervals for 24 hours in 11 postmenopausal women. Their oestriol levels were consistently low, but there was considerable variation in their oestrone and oestradiol levels both between samples and between subjects. Even where the patients had little difference between them in terms of age or duration of amenorrhoea they could have widely differing oestrogen levels, and some patients had very high levels of oestrone, similar to those found in the luteal phase of the menstrual cycle, and high levels of oestradiol, while others had very low levels of both hormones. If there is so much variation in oestrogen levels, then a very large number of subjects would be necessary to give an accurate reflection of the hormone levels of postmenopausal women, and this is another possible cause of the different results of the various studies.

Hutton et al (1978) carried out an even more intensive study, in which blood samples were taken every 20 or 30 minutes for between 4 and 24 hours from 26 postmenopausal women. They too found no relation between age or duration of amenorrhoea and mean hormone levels. They found rapid, wide and irregular fluctuation in each patient in the levels of oestrone, oestradiol, and androstenedione, with no relationship between the changes in the levels of any of the three hormones. Both Campbell (1976a) and Hutton

et al (1978) commented that single sample studies of hormone levels in postmenopausal women are invalid because of this fluctuation in hormone levels.

The role of the ovary in hormone production after the menopause was investigated by Judd et al (1974), who found that the concentration of oestrogen in the ovarian vein in post-menopausal women is little higher than that in peripheral blood, and they concluded that the ovaries make little contribution to oestrogen production after the menopause. This was confirmed by Vermeulen (1976) in a study of the effect of ACTH and HCG stimulation and dexamethasone suppression on the levels of sex hormones in post-menopausal women. He found that ACTH increased all plasma steroid levels except oestradiol, and dexamethasone significantly decreased all sex hormone levels, while HCG stimulation eventually caused an increase of borderline significance in testosterone, dehydroepiandrosterone and 17-hydroxyprogesterone levels. He concluded from this that the adrenal cortex was almost the sole source of plasma oestradiol, oestrone, and progesterone, while the ovaries contributed 50% of the testosterone and 30% of the androstenedione in the peripheral blood, and that the ovaries are not influenced by gonadotrophins after the menopause. Hemsell et al (1974) showed that oestrone, the major oestrogen of post-menopausal women, arises mainly from peripheral conversion of androstenedione. Enzymes to convert androstenedione into testosterone or oestrone, and both of these into oestradiol, are located

in many tissues. Siiteri and McDonald (1973) and Judd et al (1976) showed a positive correlation between the weight of the individual and the amount of androstenedione converted to oestrone, and Nimrod and Ryan (1975) have shown that adipose tissue plays an important part in this conversion. It does, however, seem that many factors regulate the levels of these steroids, since Chakravarti et al (1976) and Hutton et al (1978) found no clear relationship between plasma androstenedione and oestrone levels.

Both Vekemans and Robyn (1975a) and Lind et al (1978) found that prolactin levels were low in women after the menopause. Vekemans and Robyn observed that changes in prolactin levels in women paralleled changes in oestrogen levels and concluded that oestrogen must be involved in the control of prolactin secretion, but Lind disagreed with this view, as he found that the prolactin levels of his patients were unchanged by oestrogen treatment.

Menopausal symptoms are widely believed to be due to the hormonal changes of the menopause. For some years it was believed that high gonadotrophin levels caused the symptoms of the menopause, but this theory lost popularity when Fluhman (1930) and Heller et al (1944) could find no correlation between gonadotrophin levels and the severity of menopausal symptoms.

The most popular theory at the moment is that menopausal symptoms are due to oestrogen deficiency, but there is again little proof that this is the case. Several

workers have failed to show a correlation between urinary oestrogen levels and the presence of menopausal symptoms (Albright, 1936; Shute 1939) or their severity (Fluhman and Murphy, 1939; Lawrence and Moulyn, 1941) in post-menopausal women. However, Cooper et al (1974) reported that there was a correlation between plasma oestradiol levels and menopausal symptoms, with symptoms occurring when the plasma oestradiol level fell below 40 pg/ml, and being relieved when it rose above this level.

More recent research has been directed at finding a relationship between oestrogen levels and specific symptoms, rather than including all of the symptoms experienced, and this approach has proved more successful. Chakravarti et al (1979) studied the plasma hormone profiles of women approaching the menopause who were still menstruating, and reported that patients who complained of vasomotor symptoms had significantly lower plasma oestradiol levels than those expected in days 1-10 of the menstrual cycle, and had gonadotrophin levels similar to those of post-menopausal women. However, Campbell (1976a) and Hutton et al (1978) failed to show any clear relationship between either the mean levels or acute changes in plasma oestrogen concentration and hot flushes in post-menopausal women. Hutton also compared the oestrogen levels of women with dyspareunia and atrophic vaginitis with those of other post-menopausal women, and found that the women with dyspareunia had significantly lower plasma oestradiol levels than symptomless women, but there was no difference in their oestrone levels.

SOCIAL PROBLEMS OF MIDDLE AGE

The mean age at which women experience the menopause has been shown to be about 51 (Frommer, 1964; Jaszmann et al, 1969a; McKinlay et al, 1972) and around this age women experience many social changes. Some workers believe that many of the symptoms attributed to the menopause are due to social problems rather than to hormonal changes (Greenhill, 1946; Pearl and Plotz, 1964; Steiner, 1973) and it is generally agreed that these problems can exacerbate menopausal symptoms. Ballinger (1976a) found that mental disturbance in women in the perimenopausal period was associated with having elderly and dependent parents, with children leaving home, and with having problems with the children.

Elderly parents may be a great source of anxiety, as they are likely to be frail or even senile by the time their children are middle aged. Living with elderly relatives can be difficult and distressing, yet if they live alone they may be unable to look after themselves, or have an accident, and if they are admitted to residential care they feel unloved and rejected, and their children feel guilty and inadequate. The death of parents, while not unexpected, leads to feelings of grief, but illness and even death are not uncommon in middle age in both men and women, and so many women are widowed and face problems of loneliness and poverty in middle age.

Around the age of the menopause the role of mother comes to an end, as the children grow up and leave home,

and the tasks of caring for the family are no longer necessary. This means that women who have spent a large part of their lives bringing up children must develop a new life style and interests in middle age, and Van Keep and Kellerhals (1977) claim that the higher social class woman copes better than the lower class one with the menopause because she has more alternatives at her disposal in seeking a new life style. They also state that the more strongly a woman identifies with the role of mother, the more likely she is to become depressed, and Deykin et al (1966) have named this syndrome of depression after the children have left home the "empty nest syndrome".

As the children leave home, the husband and wife need to redefine their relationship. In many cases this is successful, and Deutscher (1959) reported that 22 of the 49 middle class couples he interviewed said that they found the period from age 45 to 65 more satisfactory than their earlier married life, since they had more freedom. However, Luckey and Bain (1970) found that couples who were dissatisfied with their marriage usually found their children to be a source, and sometimes their only source, of satisfaction, so such couples are likely to separate when the children grow up and leave home.

Marital problems may of course be due to the problems encountered by the husband in middle age, since men too may go through a mid-life crisis. It is often a time of stress for men at work, and if a man loses his job at this age he may have great difficulty in finding a new one. Even

if he is at the peak of his success, his energies may be concentrated on fighting off the challenge of younger men, leaving little time or energy for his home life. This increase in the time spent at work often leads his wife to believe that she is no longer attractive, and since rapid ageing is one of the commonest fears of menopausal women, this can cause great distress.

ATTITUDES AND CULTURAL INFLUENCES

The effect of the menopause is likely to be influenced by the woman's expectations, and if she is expecting to have problems then this may make them more likely to occur. The attitudes of European women to the menopause were investigated by the International Health Foundation in 1970 in a survey of 2000 women in 5 European countries. They found that 69% of these women expected the menopause to cause a physical upset, and 57% expected it to be upsetting psychologically, but 72% were glad to reach the menopause because they no longer had periods then, and no longer needed to fear pregnancy. The British women in this survey were more optimistic about the menopause than those of other countries, and only 13% of British women expected the menopause to impair their relationships with the opposite sex, and 9% to lose their attractiveness to men.

Maoz et al (1970) compared the attitudes of women of diverse ethnic origins in Israel, and found that over half of the Oriental and Arab women felt positive about the

menopause, but only 20% of the European women. They commented that women only felt positive about the menopause if they already had large families, but only worried about it if they had nothing else to worry about.

Marcha Flint (1975) suggested that the effect of the menopause depends on the change of status experienced by a woman at that time. She studied 483 Rajput women in Rajasthan, and found that few had any symptoms at the menopause other than a change in their menstrual pattern. Their status increased at the menopause, since they no longer had to remain in purdah, but were allowed to go out and to take part in the social activities of the men after the menopause. She contrasted this with the situation in America, where youth and glamour are at a premium, and the menopause is regarded as a time of loss and punishment, and where menopausal complaints are common. She suggests that menopausal complaints must be culturally defined and engendered, and that a change in the role and status of post-menopausal women could do much to reduce the frequency of menopausal symptoms in our society.

EPIDEMIOLOGY OF MENOPAUSAL SYMPTOMS

Although so many symptoms occur around the time of the menopause, we still do not know which symptoms constitute the menopausal syndrome. Donovan (1951) doubted whether there is such a syndrome, and claimed that it could be an artefact of history taking by gynaecologists. He studied 110 women diagnosed in a gynaecology clinic as

having the menopausal syndrome, and found that 95% of them had a history of decades of unexplained somatic symptoms and physical illness. Their symptoms were relieved by history taking alone in most cases, but at the next interview they complained of different symptoms. However, these results cannot be generalised to all menopausal women, as the population studied was highly selected, and patients in a gynaecology clinic are not typical of menopausal women. Hawkinson (1938) and McDowell and Paterson (1940) found a very high frequency of both physical and psychological symptoms in the menopausal patients of gynaecology clinics, and more recently Ballinger (1977) found that perimenopausal women in a gynaecology clinic had more severe psychiatric symptoms than women of the same age in the community, and were also more likely to have a history of psychiatric referral.

Many epidemiological surveys have been carried out to determine which symptoms are associated with the menopause. Their results are summarised in Table 2, and from this it can be seen that they differ markedly in their findings. All found that vasomotor symptoms are common in perimenopausal women, but estimates of their frequency vary from 35% (Jaszmann et al, 1969b) to 62% (Barrett et al, 1933), and not all enquired about night sweats. Estimates of the frequency of psychological symptoms vary widely, with the reported frequency of depression ranging from 20% (Jaszmann et al, 1969b) to 67% (Neugarten and Kraines, 1965) and anxiety from 22% (Neugarten and Kraines, 1965)

TABLE 2: Results of Epidemiological Surveys of Symptoms of Perimenopausal Women in the General Population (% reporting each symptom).

Symptom	Barrett 1933	Neugarten 1965	Jassmann 1969b	I.H.F. 1970	Thompson 1973	McKinlay 1974
<u>VASOMOTOR</u>						
Hot flushes	62	48	35	55	48	50
Night sweats	-	-	-	-	-	41
<u>PSYCHOLOGICAL</u>						
Depression		67	20	30	42	50
Anxiety		22	-	41	-	-
Irritability		82	29	29	-	-
Fatigue		80	45	43	38	-
Insomnia		46	28	32	31	36
<u>PHYSICAL</u>						
Headaches	44	59	33	38	36	41
Dizziness	40	38	9	24	19	35
Rheumatism	24	48	35	25	25	-
Palpitations	-	40	22	23	13	35
No Symptoms	16	-	-	14	-	9
Number of Women	1220	100	2956	2000	269	638
Age Range	29-91	45-54	40-60	46-55	40-60	45-54
% Postmenopausal	100	?	61	54	64	52

to 41% (International Health Foundation, 1970). This may of course reflect the difficulty in deciding which is normal and which pathological as anxiety and depression in a mild form are normal experiences, and even in a severe form may be appropriate responses to stressful events. Insomnia seems to be less common, with the lowest reported frequency being 28% (Jaszmann et al, 1969b) and the highest being 46% (Neugarten and Kraines, 1965).

It is not surprising that the surveys have produced different results, as they have each enquired about a different group of symptoms, and even where they have studied the same symptom, different wording of their questions may have given a different result, e.g. by asking about symptoms which are present now or including symptoms which were experienced in the past, and it is not clear in several of the surveys how the questions were phrased. As can be seen from Table 2, the populations had different proportions of pre- and postmenopausal women, and this is another possible cause of their differences. Barrett et al (1933) studied only postmenopausal women, and since they were aged up to 90, then it is unlikely that they would remember clearly what symptoms they had experienced at the menopause.

It is doubtful whether much can be learned about the symptoms of the menopause from this kind of study, since it gives no information on the frequency of the symptoms at other ages, and cannot show whether the symptoms are related to the menopause or to other causes. The only

study to include women of all ages was that of Neugarten and Kraines (1965) in which the prevalence of symptoms attributed to the menopause in 600 middle class American women aged between 13 and 65 was studied. They used a check-list of 28 emotional and physical symptoms, and obtained a response rate of 85%. In this study, all symptoms were reported by a number of patients in each age group, with the highest number of psychological symptoms occurring at adolescence, and the highest number of physical complaints at the menopause. Postmenopausal women had a very low incidence of all complaints. However, the actual menopausal status of the subjects in this study is not clear, since they were asked to decide for themselves whether or not they were menopausal, and some women who considered themselves menopausal were still menstruating, so the significance of these results is doubtful.

The surveys of Jaszmann et al (1969b), Thompson et al (1973), and McKinlay and Jeffreys (1974) included only middle aged women, but analysed their results in terms of menopausal age, i.e. premenopausal if they were still menstruating, menopausal if they had experienced a change in their menstrual pattern, and postmenopausal if they had amenorrhoea for more than one year. Jaszmann et al (1969b) studied the point prevalence of symptoms by sending a postal questionnaire to all women aged between 42 and 62 in the borough of Ede in the Netherlands. A total of 4584 replied, representing about 71% of the selected population, but Jaszmann gives only the results of the

2956 women who had undergone a physiological menopause within the last 10 years. He stated that a true menopausal complaint should be absent or rare before the menopause, increase in frequency at the time of the menopause, and decrease thereafter. He found that shortness of breath and emotional lability did not change in relation to menopausal age, and that irritability, fatigue, and depression were commonest in women who were still menstruating, but hot flushes, night sweats, and insomnia showed a typical menopausal pattern.

Thompson et al (1973) and McKinlay and Jefferys (1974) also surveyed the symptoms of women in the general population by means of postal questionnaires. Thompson studied 291 women aged between 40 and 60 in Aberdeen, and obtained the surprisingly high response rate of 92%, while McKinlay and Jefferys studied 955 women aged from 45 to 54 in an area of London, with a response rate of 67%. All found a similar pattern in the frequency of hot flushes in relation to the menopause. Jaszmann found that the prevalence of hot flushes increased from 17% in women who were still menstruating to a peak of 65% in the first 2 years after the menopause, and still affected 35% of women between 5 and 10 years after the menopause. Thompson found that 11% of women were having hot flushes while still menstruating regularly, compared with 79% two years after the menopause, and 20% between 7 and 9 years after the menopause, but that 93% of women experienced hot flushes at some time in the perimenopausal years. McKinlay and

Jefferys obtained results very like those of Jaszmann et al (1969b). They enquired whether their subjects had experienced hot flushes in the previous year, and found that 18% of premenopausal women, 68% of women between 4 and 5 years after the menopause, and 29% who had undergone the menopause more than 9 years beforehand reported having hot flushes.

Their results agree less closely on the frequency of insomnia. Jaszmann found that 20% of middle aged women with regular menses complained of insomnia, rising to a peak frequency of 40% in the period 2-5 years after the menopause, and remaining about 30% between 5 and 10 years after the menopause. The frequency of insomnia in relation to the menopausal age is not clear from the paper of Thompson et al (1973) but McKinlay and Jefferys found that 20% of premenopausal women complained of sleeplessness, and that the incidence of insomnia increased after the menopause but showed no clear pattern of change in relation to age, fluctuating between 32 and 58%.

There is even less agreement on the frequency of depression. Jaszmann found that 20% of premenopausal women complained of this, 24% of women with a changed menstrual pattern, and 15% between 5 and 10 years after the menopause. Thompson et al (1973) found that 33% of all age groups in their study complained of depression, and McKinlay and Jefferys found that the frequency of depression was 39% in premenopausal women, and increased to 55% immediately after the menopause, falling slightly to 45%

between 2 and 4 years after the menopause, and then increasing to 61% 7-9 years after the menopause.

These epidemiological studies have determined the prevalence rather than the incidence of symptoms, and although they have shown that many symptoms are common at this time, they have not shown whether they are due to physiological or psychological causes, or even that they are related to the menopause. However, the fact that the pattern of occurrence of insomnia, hot flushes, and psychological symptoms changes around the time of the menopause suggests that they are related to the menopause, and I have therefore investigated the effect of oestrogen treatment on these symptoms.

INSOMNIA

Sleep disturbance is common at the time of the menopause, and is usually described as difficulty in getting to sleep associated with frequent waking. There are many possible causes for this symptom. Thompson et al (1973) suggested that insomnia might be due to vasomotor symptoms such as night sweats, since many menopausal women complain that they are wakened during the night by sweats, and the changes in the frequency of these complaints around the time of the menopause are similar. Campbell (1976b) also thought that insomnia in menopausal women was due to vasomotor symptoms, since he found in his study of the efficacy of oestrogen treatment that relief of insomnia was related to improvement of vasomotor symptoms.

Age alone may account for the increase in complaints of insomnia at the menopause, as McGhie and Russell (1962), who studied the frequency of complaints of insomnia in the general population in a questionnaire survey, found that complaints of insomnia increased with age in both sexes. In men, this increase did not reach significance till the age of 65, but in women the increase commenced in middle age, suggesting that some extra factor is involved in causing sleep disturbance in middle aged women. Feinberg (1974) and Williams et al (1974) studied the relation of sleep with age using electrophysiological recording of sleep in all age groups, and they found that in older people sleep becomes more broken, with more frequent and prolonged periods of wakefulness, and less slow wave sleep than is found in young people.

Another possibility is that insomnia is due to psychological symptoms. McGhie (1966) found that insomnia is a common symptom in psychiatric illness, and Detre (1966) and Ward (1968) found that approximately two thirds of patients admitted to a psychiatric hospital complained of sleep disturbance. The relationship between sleep disturbance, psychiatric diagnosis, and mood has recently been investigated by Stonehill et al (1976) in a questionnaire survey of 375 new referrals to a psychiatric out-patient clinic. They found a high incidence of complaints of insomnia in this population, and observed that anxiety was associated with delayed sleep and late waking, endogenous depression with going to sleep early and waking early, and

neurotic depression with both initial insomnia and early waking. Mayer-Gross (1954) and Kiloh and Garside (1963) claimed that the pattern of sleep disturbance was of diagnostic significance in depressive disorders in that patients with neurotic depression complain of difficulty in getting to sleep while those with endogenous depression complain of early morning waking, but other workers have failed to show this dichotomy (Hinton, 1963; Costello and Selby, 1965). Objective studies using electrophysiological recording of sleep have failed to distinguish between the two types of depression (Hawkins and Mendels, 1966) and have shown that wakefulness actually recurs throughout the night in endogenous depression (Oswald et al, 1963).

The relationship between subjective sleep disorder, psychiatric disturbance, and the menopause has been investigated by Ballinger (1976b). She compared the pattern of sleep disturbance in women identified as "psychiatric cases" and in "non-cases" in her earlier survey (Ballinger 1975). The frequency of complaints of insomnia was considerably higher in the "cases" than the "non-cases", but in both groups there was an increase in sleep disturbance due to increased difficulty in getting to sleep in the years after the menopause. The normal women also had an increase in complaints of difficulty in staying asleep in the first six years after the menopause, with a subsequent fall, but neither group showed any significant difference in complaints of early morning waking in relation to menopausal status. Ballinger concluded from these findings

that psychological disturbance alone would not account for the increased frequency of insomnia at the time of menopause, and pointed out that the pattern of frequency of complaints of insomnia is different from the pattern of psychological morbidity, which shows a peak in the premenopausal years.

The pattern of change in the frequency of complaints of insomnia in relation to the menopause is shown in Fig. 2, and it can be seen from this that the incidence of insomnia increases as oestrogen levels fall and gonadotrophin levels rise, so it is possible that insomnia is related to the hormonal changes of the menopause. This is not of course scientific proof, and the relationship between hormones and sleep at the menopause has not yet been objectively studied, but since sleep and hormones are known to be intimately related, it would not be surprising if changing hormone levels brought about changes in sleep pattern.

HORMONES AND SLEEP

The relationship between sleep and hormones is complex, and many hormones show a change in their secretion at night, either as part of a circadian rhythm or in response to sleep. This relationship has been studied by sampling blood at intervals while sleep is being recorded electrophysiologically, and the changes in hormone levels can then be compared with the sleep pattern. The electroencephalographic appearances of sleep may be divided into sleep stages 1, 2, 3 and 4 of orthodox or NREM sleep, and

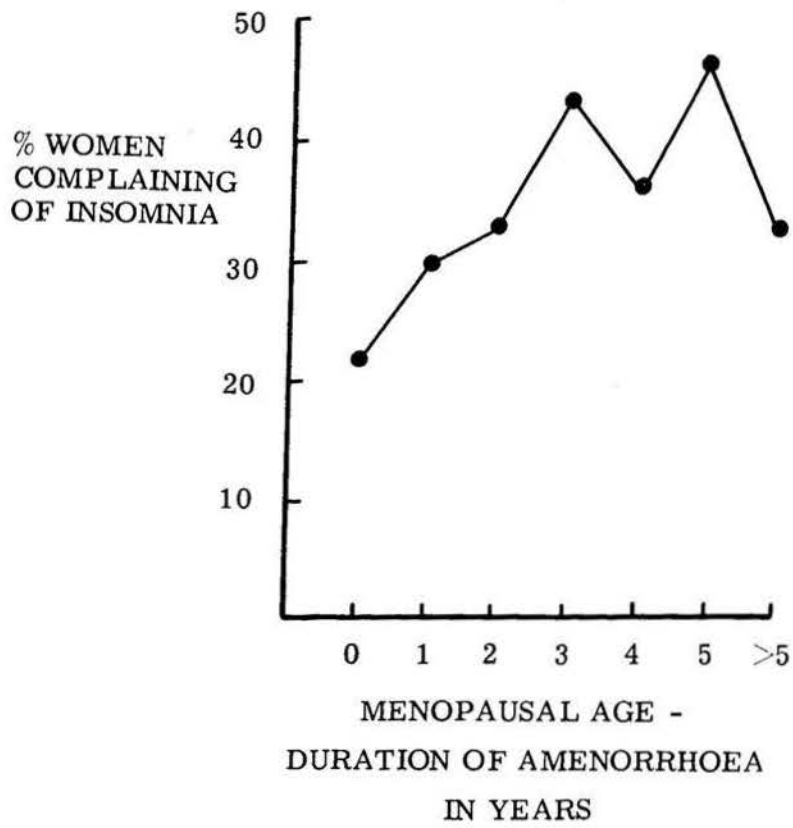


FIG. 2: Frequency of complaints of insomnia in perimenopausal women. (Jaszmann et al, 1969b).

REM or paradoxical sleep, according to recognised international criteria (Rechtschaffen and Kales, 1968). Stages 3 and 4 are known as slow wave sleep, because the EEG in these stages is characterised by large slow waves, and they occur mainly in the early part of the night. REM sleep periods recur throughout the night at intervals of approximately 90 minutes.

In some cases the hormone levels change whether or not the subject is asleep, e.g. corticosteroids, which are low at the beginning of the night but which increase just before waking due to a circadian rhythm. Other hormones show an increased secretion at night, such as thyrotropin, aldosterone, vasopressin, parathyroid hormone, growth hormone, and prolactin. In the cases of growth hormone and prolactin, this nocturnal increase is sleep dependent, and if the subject stays awake then the increased secretion is delayed until sleep onset. The increased secretion of growth hormone is associated with slow wave sleep, and the magnitude of the increase can be increased by daytime exercise or by fasting. The nocturnal secretion of prolactin is not influenced by exercise, but Vekemans and Robyn (1975b) found that the amplitude of the nocturnal prolactin peak could be reduced and its duration prolonged in young women by the administration of oestrogen. They also reported that daytime prolactin levels are low in postmenopausal women, but can be increased by oestrogen administration (Robyn and Vekemans, 1976) but they did not in this study investigate nocturnal hormone levels.

Rozencweig et al (1973) reported that the nocturnal increase in prolactin secretion showed the same pattern in post-menopausal women as is found in young men and women.

In the reproductive hormones, the clearest relation to sleep has been found around the age of puberty. Boyar et al (1972) observed an increase in the level of plasma LH at night in boys and girls around the age of puberty, and in a later study (Boyar et al, 1974) demonstrated that this increase in LH is sleep dependent and is accompanied in pubertal boys by an increase in the secretion of testosterone, and in a further paper (Boyar et al, 1976) they observed that the increase in LH in pubertal girls was accompanied by a fall in oestradiol levels in the first third of the night. This relationship between LH and sleep has also been reported in some cases of anorexia nervosa, but other than this, there is no clear evidence of a relationship between LH and sleep in adults. Boyar et al (1972) and Alford et al (1973) could find no evidence of a diurnal rhythm in LH levels nor of any change in relation to sleep in adult men, but Rubin et al (1972) claimed that LH levels were higher in REM than in non-REM periods. Results of studies of the relationship between LH and sleep in adult women too have been conflicting, since Kapen et al (1973) reported a decrease in LH levels in the first three hours of sleep in women in the follicular phase of the menstrual cycle, but not in the periovulatory phase, and Alford et al (1973) could find no evidence of a relationship between gonadotrophins, oestrogens, and sleep, though it should be noted that Alford studied only two women on day six of the menstrual cycle.

Billiard and Passouant (1974) studied sleep patterns and urinary LH and pregnanediol levels in three normal women in various phases of the menstrual cycle, but they found no changes in the sleep pattern in relation to the phases of the menstrual cycle, and no correlation between sleep and hormone levels. Hartmann (1966) has also investigated the relationship between sleep and the menstrual cycle. He recorded the sleep of four normal women and three psychiatric in-patients, two of whom were depressed, and one sociopathic, on one night per week for three months. He found that REM sleep increased in the premenstrual phase of the menstrual cycle, and suggested that this change might be due to increased progesterone levels, but the validity of this result is doubtful because of the heterogeneous nature of the population studied, in which three of the normal women suffered from premenstrual tension, and the fourth was taking the oral contraceptive pill, while the other subjects were taking amphetamines and barbiturates, which may interfere with sleep. In addition, the hormone changes of the menstrual cycle are complex, and there is no evidence to show which if any is associated with changes in sleep.

The relationship between sleep and sex hormones has also been studied by observing the changes in sleep during pregnancy, but the hormone changes of pregnancy are complex and these studies tell us little of the effects of changes in the levels of the individual hormones. Čepelák and Tůmová (1968) found that sleep duration increased in

the first trimester of pregnancy, and although this may be due to hormonal changes, it could also be due to weight gain, which is also associated with longer sleep duration. Karacan et al (1968) studied the sleep changes of late pregnancy and the puerperium by comparing the sleep of seven pregnant women with that of age-matched controls. They noted a shorter sleep duration, with more frequent arousals and less slow wave sleep in late pregnancy, followed by a rebound increase in slow wave sleep in the puerperium. Similar results were reported by Billiard and Passouant (1974). Karacan considered that the changes in sleep in pregnancy could be due to hormone changes, and he carried out a further investigation on the effect of oestrogen and progesterone treatment on a 20-year old oophorectomized woman. She was given 10 days treatment with placebo, followed by 10 days on oestrogen, then a further 10 day placebo period, then 10 days on progesterone, and her sleep was recorded on the last three nights of each period. He reported only preliminary results, which showed a slight increase in REM sleep on oestrogen, but this study is of limited value since only one subject took part, it was not a blind study, and the subject's sleep patterns may have changed with time as she adapted to the sleep laboratory.

Heuser (1968) investigated the relationship between progesterone and sleep by giving five volunteers 200 mg progesterone intramuscularly two hours before bedtime then recording their sleep electrophysiologically. He reports that the sleep latency was decreased by this treatment and

the total sleep time increased, but these results must be interpreted with caution, since Heuser gives no information on his study design and does not even say whether his volunteers are male or female, or give their ages.

Espitalier et al (1974) investigated the relationship between gonadotrophins and sleep in seven young women with secondary amenorrhoea from various causes, including one case of premature menopause. They found no relationship between FSH, LH, and sleep stages but they did find an inverse relationship between sleep duration and mean gonadotrophin levels. Their oestrogen and progesterone levels were not investigated nor did the authors study the effects of hormone treatment on these patients. Other than this, there have been no studies of the relationship between hormones and sleep at the menopause.

It is clear that studies of the relationship between sleep and reproductive hormones are at an early stage, and while the time of puberty has been intensively studied, few workers have studied adult subjects and their results have been conflicting.

Little can be learned about the relationship between sleep and hormones from studies of sleep in the menstrual cycle and during pregnancy because the hormone changes in both situations are complex, and even if changes in sleep pattern are found, it is difficult to relate them to hormone changes. Most workers have studied the effect of sleep on hormone secretion, but a few have reported the effect of hormones on sleep, and although Heuser (1968) and

Karacan et al (1968) reported that sleep duration could be increased by the administration of progesterone and oestrogen, the study design was inadequate in both cases, so these results should be interpreted with caution.

PSYCHOLOGICAL SYMPTOMS

Although emotional symptoms such as depression, anxiety, and irritability are common at the time of the menopause, it does not seem to be an aetiological factor in severe psychiatric illness requiring hospitalisation. Smith (1971) attempted to assess its significance in relation to the onset of mental illness requiring hospitalisation by comparing a patient population of 880 women with 2414 women in the general population, and since the proportion of women reaching the menopause in the previous year was the same in the two groups, he concluded that the menopause is not a causative factor of mental illness requiring hospitalisation. This was also the conclusion of Winokur (1973) in his study of 71 women admitted to hospital because of affective illness just before or after the menopause, and he calculated that the risk of developing an affective illness was no greater at this than at other ages.

The menopause does not cause involutinal melancholia, which can occur in both sexes, and has no direct temporal relationship to the menopause. Nikula-Baumann (1971) showed that there was no relationship between the hormone changes of the menopause and involutinal melancholia, since the hormone levels of cases and normal controls were

identical. The classical form of involuntional melancholia, with symptoms of restlessness, agitation, depression, anxiety, apprehension, hypochondriasis with bizarre somatic delusions, feelings of unreality, and paranoid ideas, is now rare, and it seems doubtful whether it is a discrete syndrome or merely a variant of depressive psychosis such as occurs at all ages, but coloured by the life events of middle age. Tait et al (1957) failed to find the classical symptoms of involuntional melancholia in 54 women admitted to a psychiatric hospital for the first time between the ages of 40 and 55, and Rosenthal (1968) suggested that early and effective treatment of depression may prevent the development of the full-blown syndrome.

Milder forms of psychological illness are common in the perimenopausal period, as has been shown by the epidemiological surveys reviewed in previous sections, but their cause is uncertain. Greenhill (1946) claimed that psychological symptoms at the time of the menopause are psychogenic, due to fear of the loss of fertility and the end of an active sex life, or due to an unhappy marriage, and also occur in spinsters and childless neurotics who feel that they have missed something. Stern and Prados (1946) also consider depression at the time of the menopause to be reactive, and they claim that women do not suffer from psychoneurosis at the menopause unless they have a good cause for depression or a history of mental illness.

Ballinger (1975) investigated the relationship of psychiatric morbidity to the menopause by means of the

Goldberg General Health Questionnaire, a self administered questionnaire developed to detect current emotional disturbance in community surveys. She carried out a postal survey of all women aged 40-55 on the lists of six Dundee general practitioners, and 539 (71%) of the 760 women approached responded. She identified 155 of these women as "psychiatric cases", and found an increase in psychiatric morbidity before the menopause, lasting for one year after the last menstrual period. Those women identified as cases had ailing or demanding parents, problems with the children, and children having left home more frequently than non-cases, but it was not possible to tell from this study whether the emotional problems caused the family problems, or vice-versa. Ballinger went on to interview 114 of the 155 "psychiatric cases" (Ballinger, 1976a) and found that 18 were false positives, with no evidence of psychiatric illness. In the remainder, the most common complaints were of anxiety and depression, and the commonest diagnosis was personality disorder with neurosis (69 cases) followed by affective psychosis (27 cases), while phobias and obsessional states were less common.

These results should be interpreted with caution, since the age group Ballinger studied was very limited. Hagnell (1969), in a study of the 1-year incidence of mental morbidity in the population of Southern Sweden, found that the incidence of mental illness was highest in women in the reproductive years, with a maximum at the age of 45, followed by a gradual fall to the age of 65 (see Fig. 3).

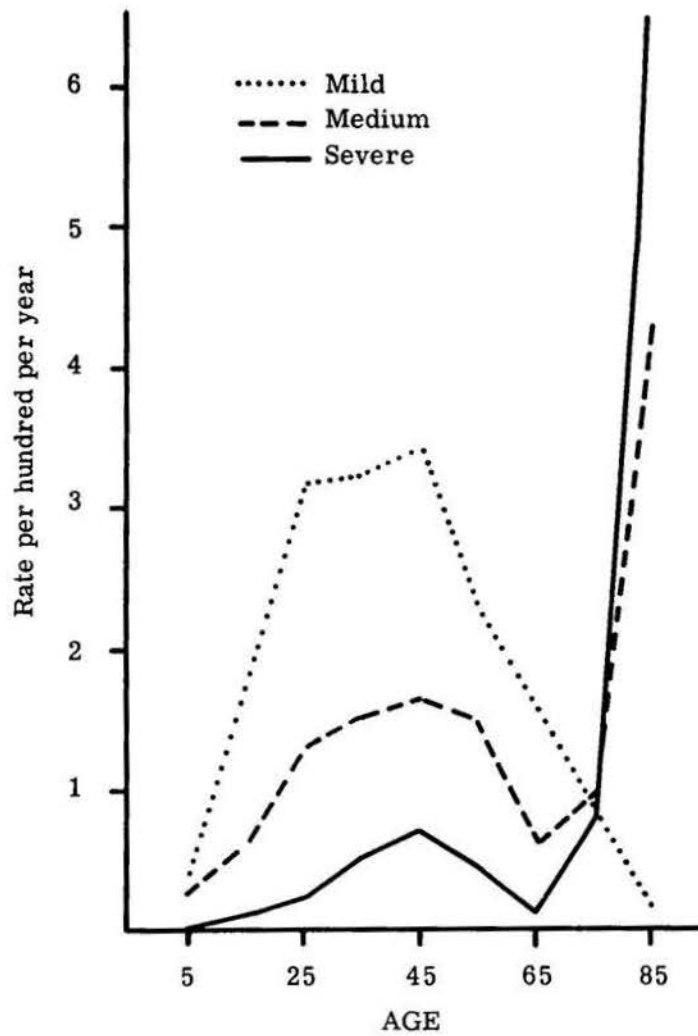


FIG. 3: The average annual incidence of onset of mental illness in women. (Hagnell, 1969)

and it is possible that if Ballinger had included younger women, she would have found that psychiatric morbidity increased at an even earlier age, or that depression or neurotic symptoms occurring at an earlier age recur at the time of the menopause.

Hallström (1973) investigated the relationship between psychological and social factors, mental health, and the menopause in middle-aged women in Gothenberg. He interviewed a stratified sample of women aged 38-54 by means of a semi-structured psychiatric interview, and examined 800 of the 899 women selected. He found no significant difference in the incidence of mental illness between the various climacteric phases but those women who developed a mental illness in the climacteric were more likely to have a family history or a previous history of mental illness, and had significantly more psychological stress factors than other women. They had more episodes of marital disruption, whether due to separation, divorce, or the death of the husband, had more problems with the children, and more unhappiness at work. He did find that women in the perimenopausal phase, which he defined as having less than twelve months amenorrhoea, complained of a deterioration in mental health more often than those in other climacteric phases in this study. Hallström also observed a decrease in the sex drive and sexual activity in middle aged women in the climacteric, which was most marked in the lower social class groups and in women with a mental illness.

Depression is approximately twice as common in women than in men during the reproductive period, and Pollitt (1977) and Weissman and Klerman (1977), who reviewed the evidence for this difference, concluded that it was most likely to be due to endocrinological factors. Symptoms of tension, depression, and irritability are known to occur in women at times of changing hormone levels, such as the premenstrual phase of the menstrual cycle, the puerperium, and when taking the oral contraceptive pill. It is widely believed that changes of mood at these times are due to changes in either the levels of oestrogen and progesterone, or in the ratio of oestrogen to progesterone, but the evidence for this is conflicting and conclusive proof is lacking. The most popular view is that depression at the time of the menopause is due to falling oestrogen levels, but again reports of this are anecdotal (Malleon, 1953; Wilson and Wilson, 1963) and proof is lacking. Utian (1972a) attempted to define the symptoms of the menopause in a study of the symptoms developed after oophorectomy by 50 South African women, compared with nine normal controls and 36 women who had had a hysterectomy with conservation of the ovaries. The patients were interviewed immediately six months and two years after the operation. He concluded that the only symptoms directly related to the oophorectomy were hot flushes and atrophic vaginitis, and that depression was likely to be of psychological origin, and was not improved by oestrogen treatment. However, these findings cannot be generalised to women undergoing a natural

menopause since the subjects had had an abrupt change in oestrogen levels due to oophorectomy, and since the post-menopausal ovary is not inert they may have had other hormonal differences. Aylward (1973) reported that both oestrogen and free plasma tryptophan levels were low in perimenopausal women and suggested that these two factors were related to depression in this age group. Coppen et al (1972) had previously reported that free plasma tryptophan levels were low in middle aged female depressives, and in a later report (Coppen et al, 1973) claimed that free plasma tryptophan levels rose as the depressed mood improved. However, other workers have failed to confirm a relationship between free plasma tryptophan and depression (Niskanen et al 1976; Peet et al, 1976; Riley and Shaw, 1976) though it should be noted that they studied patients of all ages, and the studies of Niskanen et al (1976) and Riley and Shaw (1976) included male as well as female patients.

Klaiber et al (1976) have observed that depression in women may be related to the effect of their oestrogens on the enzyme monoamine oxidase (MAO). They found that plasma MAO activity is inversely related to plasma oestrogen levels in women, and since MAO is an important enzyme in the metabolism of several of the neurotransmitters, and inhibitors of this enzyme are known to act as antidepressants, they went on to test the value of oestrogens in the treatment of depression. They carried out a controlled trial of the effect of treatment with conjugated equine oestrogens on 30 women with severe intractable endogenous depression

which had failed to respond to other forms of treatment. After three months, the 16 oestrogen treated patients had a significant decrease in their plasma MAO activity, and their score on the Hamilton depression rating scale had fallen from 29.3 to 18.4, while the 14 placebo treated patients showed no change in their MAO activity and a fall of only 1.7 in their Hamilton depression rating scale score. However, 60% of their patients were premenopausal, and the postmenopausal patients had in fact responded less well than the younger women. Also, the population studied is highly selected, and these results cannot be generalised to the mild depression which is commoner around the time of the menopause.

VASOMOTOR SYMPTOMS

The symptom most commonly attributed to the menopause is the hot flush, and as has been shown by the epidemiological surveys reviewed in a previous chapter, hot flushes start before menstruation stops in many cases, affect up to 93% of women in the years immediately after the menopause, and may even continue for up to 20 years.

Hot flushes begin with a sensation of warmth over the upper chest, spreading to the neck, face and arms, and if severe they may be accompanied by giddiness, headache, and a feeling of a wave of heat followed by profuse perspiration and a sensation of chilliness. They may occur several times a day, and a similar phenomenon, night sweats, may occur in bed. Hot flushes can be precipitated by heat, alcohol, or emotion.

Hot flushes are not merely a subjective experience, as reddening of the skin may be seen by observers. Collett (1949) observed a deeper respiration, temperature increase, and increase in basal metabolic rate during hot flushes. Molnar (1975) reported that hot flushes were preceded by tachycardia and fluctuation in the baseline of the ECG, and this was confirmed by Sturdee et al (1978). Sturdee also observed an acute rise in the skin temperature, peripheral vasodilatation, and a decreased skin resistance during the hot flush, and concluded that the hot flush is associated with a sudden and transient increase in sympathetic tone.

It is widely believed that hot flushes are due to falling oestrogen levels at the menopause. Mulley and Mitchell (1976a) reviewed the evidence for this, and stated that there was no conclusive proof of a relationship between hot flushes and oestrogen levels, but Utian (1976) disagreed with this view and stated that the response of hot flushes to oestrogen therapy proved that oestrogen deficiency causes them. Mulley and Mitchell (1976b) replied that hot flushes also respond to other treatments, including placebo, and since the superiority of oestrogen over placebo has yet to be established, it would be premature to say that response to oestrogen treatment proves a hormonal aetiology for hot flushes. Albright (1936) and Shute (1939) could find no correlation between urinary oestrogen and the severity of hot flushes. Campbell (1976a) studied the relationship between hot flushes and the changes in hormone

levels in seven postmenopausal women with hot flushes and compared them with four age-matched controls who did not experience hot flushes. He could find no difference in oestrone or oestradiol levels between his cases and controls, and although he observed that flushing patients had sharp surges of oestradiol and low baseline levels, he concluded that the correlation between hot flushes and low or falling plasma oestrogen or androstenedione levels was not close enough to prove a causal relationship. Hutton et al (1978) also compared the hormone levels of women with hot flushes with those of women without vasomotor symptoms, and concluded that flushes were not related to either acute changes or mean levels of plasma oestrogens. Not all studies of the relationship between hormone levels and vasomotor symptoms have been negative, since Chakravarti et al (1979) have recently reported that premenopausal women with vasomotor symptoms including hot flushes had lower plasma oestradiol and higher gonadotrophin levels than women of a similar age without vasomotor symptoms.

The theory that hot flushes are related to high gonadotrophin levels has little support now. Fluhman (1930) found no correlation between hot flushes and gonadotrophin levels, and recently Mulley et al (1977) reported two cases of hot flushes occurring after hypophysectomy.



TREATMENT OF MENOPAUSAL SYMPTOMS

Surprisingly few patients consult their doctors because of menopausal complaints. Newton and Odom (1964) in their study of 80 American post-menopausal women, found that only 23% consulted their doctor because of their symptoms. The International Health Foundation survey (1970) found a consultation rate of 41%, and Thompson et al (1973) found a similar rate in Dundee, where 38% of the post-menopausal women studied had consulted their doctor before their last period, and 33% had consulted him after the time of their last period. McKinlay and Jefferys (1974) found that the consultation rate among women with hot flushes was only 22% in their London study, compared to 45% in the study of Thompson et al (1973).

This low consultation rate may be due to the mild nature of the symptoms, and the IHF survey found that 88% of the women who did not consult their doctor said they would do so if their symptoms became troublesome, and only 9% said that 'nature must take its course'. McKinlay and Jefferys too found that women were more likely to consult their doctor if they experienced acute physical discomfort and embarrassment from their symptoms.

The difference in consulting rates may also reflect the attitudes of the doctors, since not all agree that menopausal symptoms require treatment, and those who do recommend treatment are divided in their opinions of the most appropriate treatment.

Some favour psychotherapy as being the best form of treatment, but others recommend drug treatments such as tranquillisers, antidepressants, or hormone therapy. Many of the papers recommending these treatments are purely anecdotal, and give no evidence or data to support the argument, but a large number of clinical trials have also been carried out. It is still not possible to draw any firm conclusions about the treatment of the menopause, since these clinical trials have not produced comparable or consistent data. They differ in the treatments and doses used, and in the symptoms studied, and many have used only crude global ratings including all symptoms, and in some cases side effects too, as a measure of change. The Blatt (or Kuppermann) Menopausal Index was devised by Kuppermann et al (1953) in an attempt to increase the comparability of results, and it is a rating scale which includes a number of symptoms which are common at the time of the menopause, giving extra weighting to the more common symptoms such as hot flushes (see Fig. 4). It has been used in many studies, but its value is in question because several of the symptoms included, such as headaches and palpitations, are not now considered to be associated with the menopause.

A further problem in evaluating clinical trials is the heterogeneous population studied, including women who are still menstruating, women up to 30 years post-menopausal, and women who have undergone hysterectomy and oophorectomy.

Symptoms	Weighting Factor	Severity	Score
1. Vasomotor	4		
2. Paraesthesiae	2		
3. Insomnia	2		
4. Nervousness	2		
5. Depression	1		
6. Vertigo	1		
7. Fatigue	1		
8. Bone and Joint Pain	1		
9. Headaches	1		
10. Palpitations	1		
11. Formication	1		

FIG. 4: Menopausal Index Rating Scale (Kupperman et al, 1953)
 The severity of each symptom is rated on a 4-point scale and multiplied by the appropriate weighting factor, and the sum of these scores gives the menopausal index score.

A marked and prolonged placebo effect on menopausal symptoms has been reported by Pratt and Thomas (1937), Donovan (1951) and Coope et al (1975), but many studies have lacked a control group, or been inadequately controlled.

(a) Psychotherapy

Controlled trials of psychotherapy are almost impossible to devise, though this treatment has repeatedly been reported to be effective in relieving menopausal symptoms (Saunders, 1932; McDowell and Paterson, 1940; Hoskins, 1944; Greenhill, 1946; Fessler, 1950; Williams, 1971).

Pearl and Plotz (1964) see the aim of treatment as facilitating adjustment to a natural change, and consider that this can best be done by supporting, reassuring, and educating the patient, correcting her fantasies, and urging her to use her new freedom from family concerns to extend her activities, reactivate dormant interests, and pursue unfulfilled ambitions. McCandless (1964) and Steiner (1973) advocate the use of marital therapy as well as individual psychotherapy, since the changes of middle life can bring difficulties to both partners in a marriage. Donovan (1951), who relieved most of his patients' symptoms by history taking alone, states that the most important factor in relieving menopausal symptoms is a good doctor-patient relationship, and Jeffcoate (1960) claims that explanation, advice, and reassurance will alleviate or prevent menopausal symptoms in 95% of menopausal women, and that only those who are over-anxious require medication.

Most of those who advocate psychotherapy do so on the basis of clinical impression rather than scientific study, and so their papers are mainly anecdotal. Donovan is the only one to give data, and he was not giving psychotherapy, but merely taking a case history.

(b) Tranquillisers and Antidepressants

These are frequently prescribed, but seldom studied, in the treatment of menopausal symptoms. Jeffcoate (1960) recommends their use for women with symptoms of irritability and emotional upset who have not responded to psychotherapy, and claims that they will also reduce vasomotor instability. Pearl and Plotz (1964) endorse this recommendation and further state that the somewhat noxious mixture of phenobarbitone, belladonna, and ergotamine tartrate, should be given on a temporary basis to the severely distressed patient. No data to support the recommendations is given in either of these papers.

Three studies on the use of antidepressants have been carried out, by Forman (1968), Kerr (1970) and Wheatley (1977). Forman reported a double-blind study comparing an antidepressant (amitriptyline) with a tranquilliser-antidepressant combination (amitriptyline-perphenazine) on 26 women. He concluded that the combination was more effective, since 16 patients improved on this compared with seven on amitriptyline alone, but the value of this conclusion is doubtful since improvement was measured by a crude global scale including relief from all symptoms and

the presence of side effects, and no data is given on the composition of the two treatment groups or the dose of drugs used. Since no control group was included in this study, it is not possible to tell whether these two treatments were more effective than placebo in relieving symptoms. Kerr (1970) reported a double-blind study of amitriptyline against placebo in 50 women with 'emotional change'. The characteristics of the groups again are not reported, and emotional and physical symptoms were rated together on a global scale from 0-4. Kerr concluded that amitriptyline improves emotional symptoms in the menopause, since 76% of the treatment group improved, compared with only 25% of the placebo group, but the value of this conclusion is doubtful, because of the confused nature of the treatment regime. He gave varying doses of amitriptyline, according to the response, but the mean dose was very low (55 mg/day), and the results were further confused by the administration of oestrogen therapy, again in two different doses, to both treatment and control groups.

Wheatley (1977) compared the effect of amitriptyline (25-50 mg. T.I.D.) with or without the addition of 3 mg/day piperazine oestrone sulphate on 58 depressed menopausal women. He found that all improved, and that the addition of oestrogen did not produce any significant additional improvement as measured by the Hamilton rating scale, global rating, or a self-rating scale.

These studies, then, have failed to demonstrate that antidepressants are significantly more effective than

placebo in treating depression in the menopause because of their inadequate controls.

(c) Hormone Therapy

A variety of hormones, including oestrogens, androgens, and progesterone, have been used either singly or in combination in the treatment of the menopausal syndrome. The most widely used hormone treatment is oestrogen, which may be given orally, by injection, or as a depot in the form of a subcutaneous pellet. Oestrogens may be classified as natural (oestrone, oestradiol, oestriol), conjugated (equine oestrogens) and synthetic (ethinyl oestradiol, stilboestrol) and it has been claimed that the natural oestrogens are safer than the synthetic, though this has not been conclusively proven. Progesterone is usually given cyclically in combination with oestrogen to produce a withdrawal bleed, intended to minimise the risk of endometrial hypertrophy or carcinoma, and testosterone, which may in large doses have a virilizing effect, is sometimes given to menopausal women to increase libido and produce a sense of well-being.

Oestrogen treatment is frequently called hormone replacement therapy, but this term is misleading, since it implies that the hormones are returned to premenopausal levels. It is known to reduce gonadotrophin levels, but both Larsson-Cohn et al (1977) and Lind et al (1978) have found that gonadotrophin levels of women on oestrogen treatment remained higher than those of premenopausal women. Many workers have showed that oestrogen treatment causes

an increase in both oestrone and oestradiol levels (Cooper et al, 1974; Daw, 1975; Aylward, 1976; Hutton et al, 1977; Larsson-Cohn et al, 1977; Lind et al, 1978). Most of these workers have studied the effect of piperazine oestrone sulphate, oestradiol valerate, or equine oestrogens, and with these treatments it seems that there is a very high level of oestrone at the start of treatment (Jacobs et al, 1977; Anderson et al, 1978) while oestradiol levels increase only gradually, and the levels of both oestrogens stabilised at the end of a months treatment. The actual oestrogen levels depend on the dose and the type of oestrogen used, but it is surprising to find that piperazine oestrone sulphate and oestradiol valerate have the same effect on plasma oestrone and oestradiol levels, as was reported by Hutton et al (1977), Jacobs et al (1977), and Anderson et al (1978). These authors concluded that oestradiol must be converted into oestrone either in the gut or in the liver, and it seems that treatment with these two oestrogen preparations must have the same effect. However, not all oestrogen preparations have the same effect on plasma oestrogen levels, and Larsson-Cohn et al (1977) found that oestradiol valerianate and ethinyl oestradiol had different effects on both gonadotrophin and oestrone levels in post-menopausal women. Although many of these workers have found that oestrogen treatment can restore plasma oestrogen levels to those found in the menstrual cycle, none have found that the cyclic pattern of change in the levels was restored, or that the premenopausal oestrone:oestradiol

ratio was restored. Before the menopause, this ratio is less than one, but in postmenopausal women the levels of oestrone exceed those of oestradiol, and oestrogen treatment has been found to leave this ratio unchanged (Lind et al, 1978) or even to increase it (Jacobs et al, 1977; Larsson-Cohn et al, 1977).

Many authors have given advice on the use of oestrogen treatment, but given no evidence to support their views (Novak, 1940; Connon, 1973; Kerr and Vaughan, 1975). Wilson and Wilson (1963) have claimed that the menopause is a deficiency disease, to be treated with oestrogen from the onset of irregular periods till death, and they believe that this treatment will prolong youthfulness and good health, but few would agree with the extreme view. It is generally agreed that oestrogen treatment relieves atrophic vaginitis, and Lindsay et al (1976) and Horsman et al (1977) have reported that oestrogen treatment can stop and perhaps even reverse osteoporosis in postmenopausal women, but its value in the treatment of other menopausal symptoms has yet to be conclusively proven. Since there is no agreement on which symptoms are related to the menopause, studies in which the symptoms have been rated on scales which include several symptoms have given little information on the value of hormone therapy. The symptom which has most commonly been studied is the hot flush, since this is the symptom most commonly attributed to the menopause, but even here the value of oestrogen therapy is controversial. Cross-over studies carried out by

Greenblatt et al (1950), Kupperman et al (1953), Utian (1972a), Coope et al (1975) and Campbell (1976b) have all shown that oestrogen is significantly more effective than placebo in relieving hot flushes. However, Mulley and Mitchell (1976) concluded that the value of oestrogen treatment in the treatment of hot flushes has not been conclusively proven, since other workers found no difference between oestrogen and placebo, and several of the studies which did report a difference had design flaws such as lack of double-blindness, or inadequate controls.

Other workers have been so convinced of the value of oestrogen treatment that they have not included a control group in their studies e.g. Reich et al (1952), Wallach and Henneman (1959), Wilson et al (1963), Tramont (1966), Perrell and Bennett (1970), Schleyer-Saunders (1971), Villadolid et al (1973) and Rhoades (1974). These have all concluded that oestrogen relieves menopausal symptoms, but because of the lack of a control group, they have failed to prove that it is more effective than placebo.

The studies of Lozman et al (1971), Aylward et al (1974) and Wheatley (1977) have also been inadequately controlled, since they gave their patients a placebo followed by two oestrogen treatments in a cross-over design, but did not include placebo in the cross-over part of the study.

Other workers have included a placebo period in their cross-over studies (Greenblatt et al, 1950; Coope et al, 1975; Campbell, 1976b) and these have all found that

oestrogen is more effective than placebo in relieving menopausal symptoms. The study of Campbell is of particular interest since he investigated a number of physical and psychological symptoms individually. He actually carried out two studies, one on patients with mild symptoms and one on patients with severe symptoms. The study of the patients with mild symptoms lasted for one year, during which the patients took conjugated equine oestrogens for three out of four weeks for six months, and placebo for six months, but the study of the patients with severe symptoms lasted for only four months, two on active treatment and two on placebo. The patients in both studies were assessed every two months using the Goldberg general health questionnaire (GHQ), Beck depression self-rating scale, and the Eysenck personality inventory (EPI), as well as self-rated graphic rating scales for a wide variety of symptoms. The GHQ, Beck scale, and EPI all showed a marked placebo effect and failed to differentiate between the oestrogen and placebo treatments, but the graphic rating scales showed oestrogen to be more effective than placebo in relieving hot flushes, vaginal dryness, and poor memory in the patients with mild symptoms, and hot flushes, insomnia, vaginal dryness, irritability, and headaches in the group with severe symptoms. Coope et al (1975) found no significant difference between the oestrogen treated patients and placebo treated patients in the first part of the study, but after the cross-over oestrogen was significantly more effective than placebo.

The results of these cross-over studies should be interpreted with caution, since the patients may have had persistently elevated oestrogen levels after the cross-over from oestrogen to placebo treatment. Daw (1975) found that after three months treatment with piperazine oestrone sulphate the oestradiol levels in plasma remained above the pretreatment levels for three months, and since both Coope et al (1975) and Campbell (1976_b) allowed only a one week withdrawal period before the cross-over, the patients may not have returned to the baseline condition.

Other studies have compared the effect of oestrogen and placebo on menopausal women. The earliest of these was the study of Pratt and Thomas (1937), in which the effect of theelin (an oestrogen preparation given by i.m. injection) was compared with the effect of a placebo oil injection, and phenobarbitone tablets with placebo tablets. The majority of the patients improved regardless of the nature of the treatment, and they found the various treatments to be equally effective in relieving both physical and psychological symptoms. It should be noted that 50% of the patients dropped out from this study, and although the authors claimed that this was usually because they felt well, they give no data to support this. Järvinen et al (1971) carried out a similar study comparing oestriol succinate with placebo, and they also failed to show that the oestrogen was more effective than the placebo treatment. Martin et al (1971) compared a sequential oestrogen-progestagen combination with placebo, and concluded that

oestrogen was significantly more effective than placebo in relieving hot flushes, but their study was unlikely to have been double-blind, since the patients had withdrawal bleeding at the end of every month on active treatment.

Cooper et al (1974) compared the effect of placebo and piperazine oestrone sulphate on oophorectomized women. In their study, the control group showed no improvement, while the oestrone group had relief of symptoms in nine out of ten cases, though there was no clear cut level of oestrogen at which symptoms were abolished. In a further investigation, Daw (1975) studied both nine oophorectomized women and eight women with a physiological menopause, all of whom were given oestrogen treatment for three months. In general, patients with less than 40 pg/ml plasma oestradiol had symptoms, and those with higher levels had not, though the cut-off was not in fact as clear as this. Following cessation of treatment, plasma oestradiol levels remain elevated for twelve weeks before showing a steady fall, and symptoms recurred when oestradiol levels fell below 40 pg/ml. This study was uncontrolled, and, as with the previous study, no information is given on the nature of the symptoms, nor how they were rated.

Many attempts have been made to treat mental illness in postmenopausal women with oestrogens, but these have met with little success. Severinghaus (1933) found that oestrogen injections combined with psychotherapy improved psychological symptoms in 32 postmenopausal women, and Hawkinson (1938) reported excellent results in relieving

depression in 1000 postmenopausal women and further claimed to have cured 12 out of 14 women with depressive illness by ten weeks of oestrogen therapy, but other studies have produced conflicting results. Bowman and Bender (1932) found that only two out of their seven cases of involutional melancholia improved, and Shube et al (1937) found no improvement in ten cases. The only controlled study was that of Werner et al (1936), but this trial was not blind, and the control group were also given oestrogen treatment after six months. They reported a final improvement rate of 29 out of 40 cases, but many of these may have improved spontaneously, and this study was inadequately controlled. Oestrogen therapy never became widely accepted as a treatment for depressive illness, and with the advent of effective antidepressants its use was abandoned. However, its use in milder cases of depression continues, although the results of therapeutic trials have been conflicting.

The effect of oestrogen treatment on psychological symptoms has been studied by many workers, but their results have been conflicting. Utian (1972b) carried out a single-blind cross-over study of the effect of equine oestrogens on oophorectomized women in which their emotional state was rated using a 6-point global rating scale, in which the patient's account, and where possible her husband's account, of how she was coping at home, at work, and socially were assessed. He observed that oestrogen had a mental tonic effect, but when George et al (1973) attempted to replicate this work using the Beck self rating scale of depression to

measure mood, they found that oestrogen was no more effective than placebo in improving mood. They concluded that the mental tonic effect was dose-dependant, since they had used a smaller dose of oestrogen than that used by Utian (1972b), but Hawkins and Polakow (1974) pointed out that George et al (1973) had only studied 13 patients, and that this is too small a group to show statistically significant results.

Aylward (1973) also found that oestrogen treatment improved depression in his double-blind controlled study of the effect of piperazine oestrone sulphate on the mood of oophorectomized women. At the start of his study, all patients had low free plasma tryptophan levels, and oestrogen treatment was associated with an increase in the free plasma tryptophan levels and relief of depression, while the placebo group had persistently low free plasma tryptophan levels and remained depressed. In a later paper (Aylward, 1976) he reported that a double-blind controlled study had showed that piperazine oestrone sulphate was significantly more effective than placebo in relieving depression in 65 postmenopausal patients, but since he had treated all patients with placebo before the start of the study and eliminated all placebo responders, this result is scarcely surprising. It is arguable whether or not it is justifiable to exclude placebo responders from a study, and a further problem in evaluating these two studies is the lack of information about the actual scores of the patients on the Hamilton depression rating scale.

The effect of oestradiol valerate on depression in postmenopausal women was studied by Fedor-Freybergh (1977). He carried out a double-blind controlled study on 21 patients in which they were assessed, given a supply of tablets which they were told would help them, and reviewed at the end of three months. The placebo group (n=10) had showed an increase in their mean score on the Hamilton depression rating scale, but the oestrogen treated group (n=11) showed a significant fall in their scores. Neuroticism as measured by the Eysenck personality inventory also fell in the oestrogen treated patients, and increased in the placebo group, and on a general health questionnaire the patients on active treatment also reported an improvement in anxiety, sleep, and memory.

The studies of the effect of oestrogen treatment on psychological symptoms at the time of the menopause have not all shown oestrogen to be more effective than placebo. Utian (1972a) and Rauramo et al (1976) both compared the effect of oestrogen and placebo on women after oophorectomy in an attempt to determine the relationship between the symptoms developed and the change in oestrogen levels. Utian observed that depression, irritability, and insomnia were significantly relieved by placebo and concluded that these symptoms must be psychogenic in origin, since oestrogen was no more effective than placebo in relieving them. Rauramo also found that oestrogen was no more effective than placebo in relieving depression and anxiety after oophorectomy, but he found that the oestrogen

treated group had a lower incidence of complaints of insomnia. Pratt and Thomas (1937), as already mentioned, failed to show the superiority of oestrogen over placebo in relieving psychological symptoms in postmenopausal women, and in cross-over studies both George et al (1973) and Campbell (1976b) found that oestrogen was not significantly more effective than placebo in relieving depression in postmenopausal women. Strickler et al (1977) also carried out a cross-over study of the effect of equine oestrogens on psychological symptoms in postmenopausal women, and found that 16 of their 20 patients responded equally to oestrogen and placebo, and only two responded to oestrogen and not to placebo treatment, so they too failed to show that oestrogen is the more effective treatment.

It is clear from this review of the literature that little is yet known about the menopause and the symptoms associated with it, and that oestrogen treatment can only be evaluated by investigating its effect on individual symptoms rather than a group of complaints which may be unrelated to the menopause. There are likely to be differences between women who have undergone a surgical menopause, perimenopausal women, and women who are 20 or 30 years postmenopausal, so in order to study a homogeneous population, the age range included in any study should be limited. In view of this, I have investigated the effect of treatment with piperazine oestrone sulphate on sleep, mood, anxiety, and hot flushes in perimenopausal women.

SUBJECTS MATERIALS AND METHODS

Patients in this study were either referred by their general practitioners or, in a small number of cases, had volunteered after hearing about the study from their friends. All patients taking part in the study did so with the knowledge and consent of their general practitioner. The patients were women aged 45-55, with amenorrhoea for at least three months, and symptoms of insomnia, depression, anxiety, and hot flushes, who had no contra-indication to oestrogen therapy such as a history of thrombo-embolic disorders, malignancy, or jaundice. Before commencing the study, all patients were interviewed so that the study could be explained to them and a full history taken, and they were shown the sleep laboratory. Anyone taking hypnotics, tranquillisers, or hormone therapy was required to undergo a 6-week withdrawal period before starting the trial. All subjects received £4 per night for travelling expenses.

The trial was double-blind and controlled, and lasted 14 weeks for each patient. In the first six weeks all patients received a placebo, but in the remaining eight weeks half of the patients (designated the oestrone group) received piperazine oestrone sulphate ("Harmogen") in a dose of 1.5 mg twice daily, while the remaining patients (the placebo group) remained on placebo throughout the study as a control. Oestrogen and placebo tablets were identical in appearance and were labelled with a code so that the patients and staff were unaware of their content.

All patients were warned that the pills they received might be blanks.

Throughout the study, patients attended the sleep laboratory in pairs on one night per week for electrophysiological recording of sleep. In each pair, one patient was in the oestrone group and one in the placebo group. Patients reported to the sleep laboratory at 9 p.m. and, after preparing for bed, had silver disc electrodes attached to the frontal bosses and the outer canthi for eye movement monitoring. Electrodes were placed in the mid-line, F-C-P distribution of the international 10/20 system of electrode placement to give an EEG record, and submental electrodes were used to record muscle tone (see Fig. 5). The patients retired to single bedrooms, and the lights were switched out at 22.30 and recording was carried out from 22.30 to 07.15.

The first two nights in the sleep laboratory were for adaption purposes only, because of the first night effect (Agnew et al, 1966) which decreases REM and slow wave sleep, and increases the number of shifts to wakefulness. The next four nights, when all patients were receiving placebo, were in the baseline period, the next four in the first treatment month, and the remaining four in the second treatment month. Ultimately the sleep records were scored blind according to standard international criteria (Rechtschaffen and Kales, 1968) into wakefulness and sleep stages 1, 2, 3, 4 and REM. Wakefulness is characterised by low voltage fast activity and α rhythm in the EEG, high

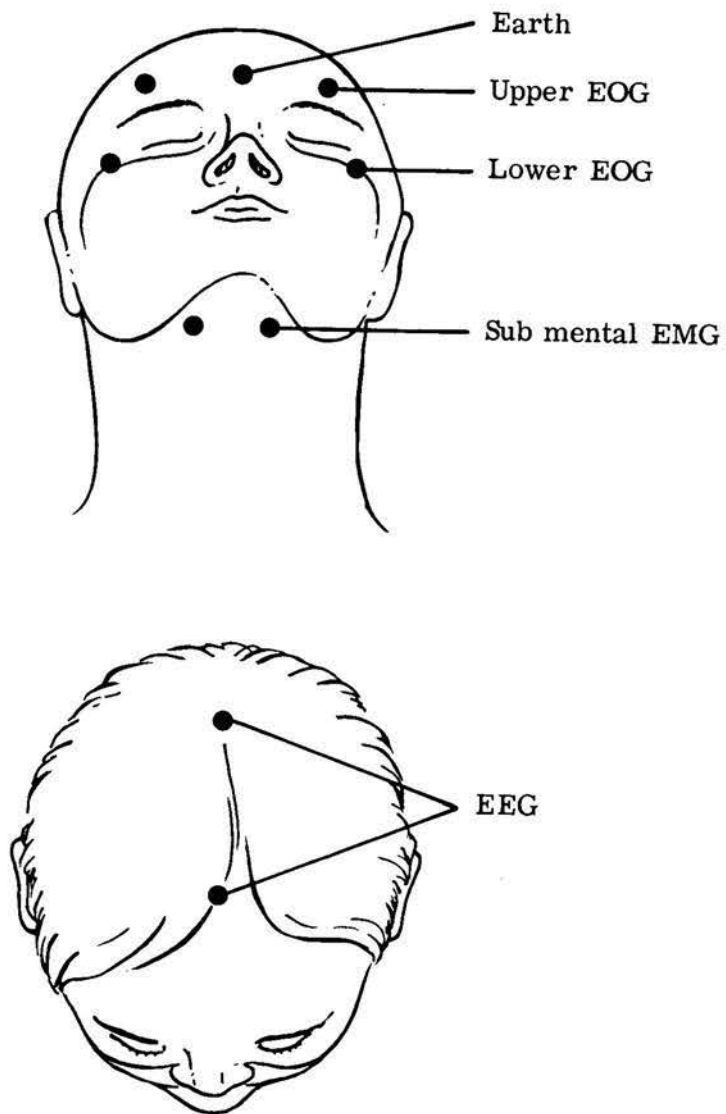


FIG. 5: The position of electrodes for electrophysiological recording of sleep.

muscle tone, frequent movements, and blinking of the eyes (see Fig. 6). As the subject passes from wakefulness to sleep there is a gradual slowing of the EEG activity. The low voltage fast activity of wakefulness is replaced by mixed frequency waves predominantly in the 2-7 Hz band in stage 1 sleep. In stage 1 there are less than 50% Δ waves in the EEG, no sleep spindles or K complexes, and slow rolling movements of the eyes (see Fig. 7). After a while, eye movements cease and bursts of 12-14 Hz sinusoidal waves, known as sleep spindles, and isolated biphasic high voltage waves called K complexes appear in the EEG. This indicates that the subject has passed into stage 2. The characteristic features of this stage are shown in Fig. 8. When high voltage delta waves of 0.5 -2.5 Hz appear and occupy more than 20% of the EEG recording, the subject is in stage 3 sleep (see Fig. 9), and when delta waves occupy more than 50% in stage 4 sleep (see Fig. 10). Sleep stages 3 and 4 are known as slow wave sleep because of their typical EEG pattern, and these stages occur mainly in the first few hours of sleep. Sleep stages 1-4 are known as Non-REM sleep.

REM sleep recurs at intervals during the night. In this stage of sleep the EEG changes to a low voltage mixed frequency pattern, and may show Δ rhythm and waves of 2-3 Hz with a notched appearance known as saw tooth waves (see Fig. 11). The EMG shows low muscle tone with occasional muscle twitches, and the characteristic eye movements appear (see Fig. 11). REM sleep recurs at intervals of approximately 90 min throughout the night, and there are

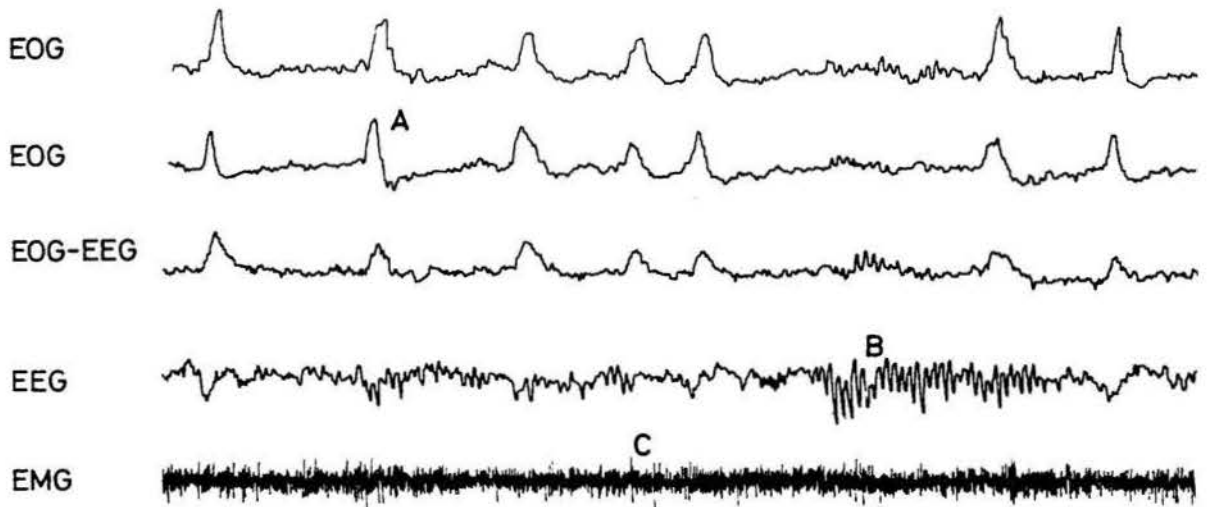


FIG. 6: Sleep record during wakefulness.

A = Eye blink in the EOG

B = α rhythm in the EEG

C = High muscle tone

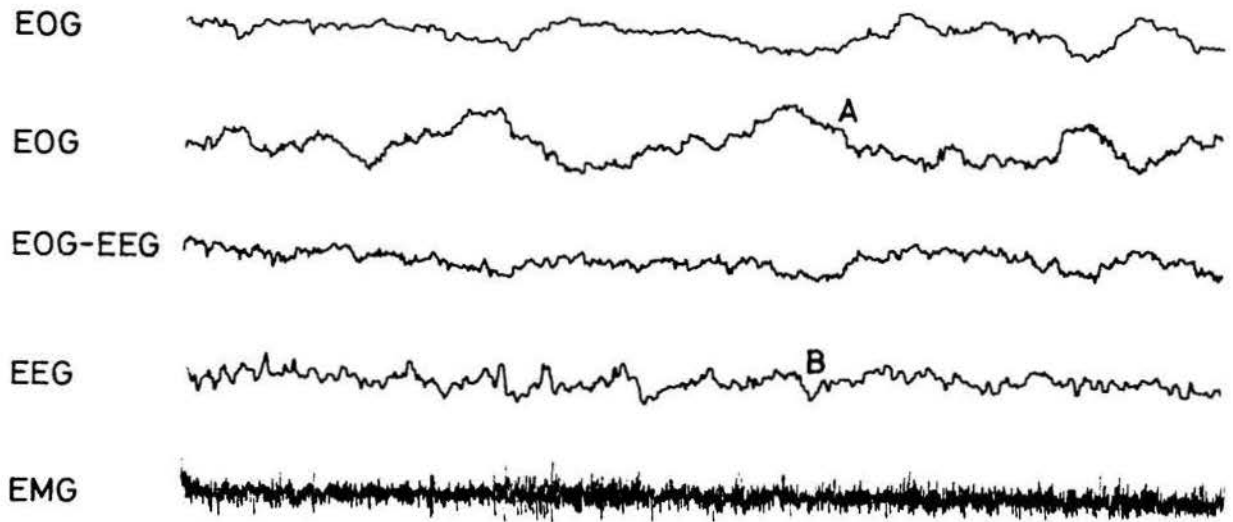


FIG. 7: Sleep record showing stage 1 sleep (drowsiness)
A = Rolling eye movements
B = Low voltage mixed frequency EEG pattern

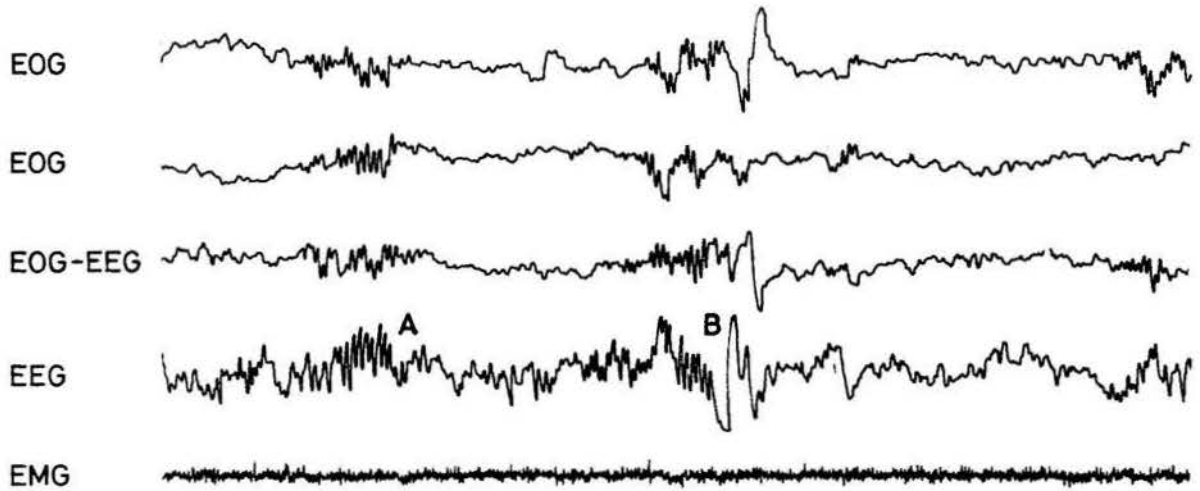


FIG. 8: Sleep record during stage 2 sleep.

A = Sleep spindles

B = Sleep spindles followed immediately by a
K-complex

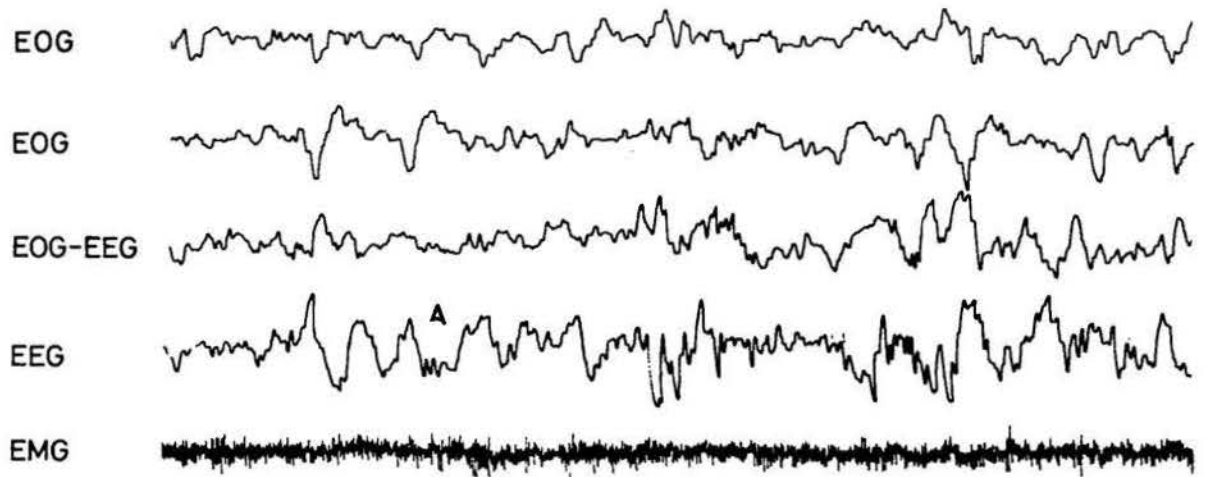


FIG. 9: Sleep record during stage 3 sleep.
A = delta wave activity in EEG

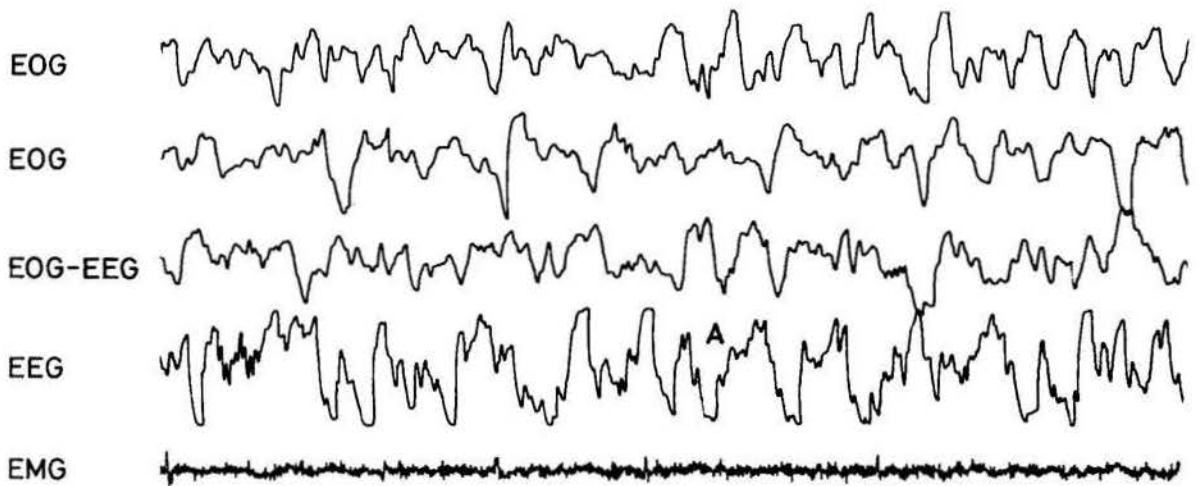


FIG. 10: Sleep record during stage 4 sleep.
A = delta wave activity

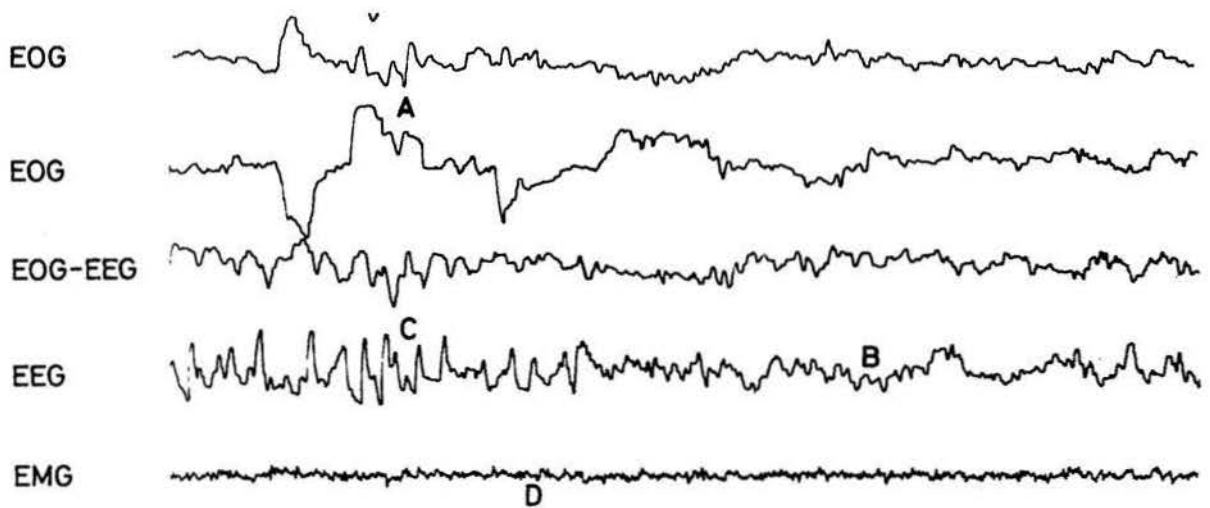


FIG. 11: Sleep record during REM sleep.

A = Rapid eye movement in EOG

B = Low voltage EEG

C = Saw tooth waves in EEG

D = Low muscle tone

usually between four and six REM periods per night. As the night progresses, the REM periods become longer so there is a higher proportion of REM sleep in the later hours of sleep.

When recording was complete, the sleep records were scored visually in 20-second epochs, and a computer programme was used to calculate the total sleep duration, sleep onset latency, sleep stage data, stage changes, and REM latency for each night. Sleep stage changes and the amount of each sleep stage in the first six hours of sleep were also calculated. The changes between the baseline period and the first treatment month and baseline and second treatment month were examined and the magnitude of the change in the two groups compared using a Student's t test. A 1-tailed test was used for intervening wakefulness and number of arousals, which we had predicted would decrease on oestrogen treatment, and a 2-tailed test was used in all other cases. Intra-group changes in the different periods of the experiment were compared using a t test for paired observations.

Patients rated their sleep quality, mood, and anxiety levels daily throughout the study using 10 cm line visual analogue scales. The left hand end of the sleep quality scale was labelled "best ever" and the right hand end "worst ever". Patients were told that the centre of the line approximated to a normal night sleep, and that each morning they should make a mark to indicate how well they had slept compared to a normal night's sleep.

The remaining scales of mood and anxiety were completed in the evening to show how the patient had felt during that day. The mood scale was marked "most depressed ever" at one end and "most cheerful ever" at the other end (see Fig. 12), and the anxiety scale ran from "terribly agitated" to "imperturbable tranquillity".

Visual analogue scales were scored by measuring the distance from the left hand end of the line to the mark in millimetres. The mean weekly score for each subject and for each group were calculated, and also the mean scores for the baseline period, first treatment month, and second treatment month. The difference of the weekly mean from the baseline mean was plotted graphically for each week of the study in each group and the patterns compared. The mean scores in the three periods of the study, and the changes in score of the two groups, were compared using *t* tests as described for the sleep studies.

Observer rating scales of depression (Hamilton, 1960) and anxiety (Hamilton, 1959) were completed at the beginning and end of the baseline period, the end of the first treatment month, and the end of the second treatment month. Examples of each rating scale are given in appendix 1. The mean score on each scale was calculated for each group at each assessment point, and these were plotted graphically to show the changes in each group throughout the study. The significance of the changes in each group was evaluated using a *t* test for paired observations, and the magnitude of the changes in the oestrone and placebo groups compared using a Student's *t* test.

MOOD

NAME DATE

Please indicate, by a mark on the line, how you felt in your spirits today. If you have felt more lively and cheery than usual you should make your mark to the right of the centre, if more listless and gloomy than usual, your mark should be to the left. An average day should mean a mark in the centre.

Most depressed
everMost cheerful
ever

FIG. 12: Visual analogue rating scale of mood.

Each patient was asked to note the number of hot flushes experienced in the previous 24 hours at the end of each day. Total weekly hot flush counts were calculated for each patient and group means for each week and each period of the study determined. The mean weekly hot flush count for the oestrone and placebo groups were plotted graphically, and the significance of the changes between the three periods of the study and between the two groups was determined using t tests as previously described.

The patients were also asked to complete a visual analogue scale of hot flush severity at the end of each day. This scale was a 10 cm line with "no flushes" at the left hand end and "very bad, couldn't be worse" at the right hand end. The scale was scored by measuring the distance from the left hand end of the line to the mark made by the patient in millimetres, and the results analysed as for the other visual analogue scales, described above.

NEUROENDOCRINE STUDIES

Twelve volunteers attended the sleep laboratory on two extra nights, one in the baseline period and one at the end of the first treatment month, for blood studies. On these occasions, a catheter was inserted into a forearm vein and filled with heparinised saline (10,000 units heparin in 500 ml 0.9% saline), and electrodes were then attached in the usual way for electrophysiological recording of sleep. When the patient retired to bed, the catheter was connected to a catheter extension filled with

heparinised saline which passed through the bedroom wall into the next room, so that blood samples could be taken without disturbing the patient. Sleep was recorded as usual, and blood samples were taken at 20 minute intervals throughout the night. When taking a blood sample, the catheter and catheter extension were first cleared by withdrawing a volume of fluid just greater than that required to fill them (this volume was measured while assembling the system), then a 10 ml blood sample was taken and the catheter and catheter extension were cleared of blood by injecting sufficient heparinised saline to fill them, and the system was sealed until the time of the next blood sample. The sleep record was marked at the start and end of each blood sample, to facilitate the correlation of blood levels with sleep stages. The blood sample was centrifuged immediately, and the plasma was separated and stored at -20°C until assayed.

Each sample was assayed for oestrone, oestradiol, prolactin, and free and total plasma tryptophan. Oestriol levels in menopausal women are known to be low, and since a larger blood sample would have been required for oestriol assays it was decided that oestriol assays would not be justified. The oestrogens were extracted from plasma with diethyl ether and separated by IH-20 column chromatography. Oestrone and oestradiol concentrations were then measured by radioimmunoassay (Kirkham and Hunter, 1971; Abraham, 1974) using standard antisera prepared in sheep against oestradiol- 17β succinyl albumin (New England Nuclear).

The antisera had 50% cross-reactivity with oestrone, but since the oestrogens were separated before assay, each could be measured against the same antiserum, using appropriate standards. The coefficient of variation of this method, based on the use of frozen pooled serum assayed 32 times, was 14%. Prolactin was measured by radioimmunoassay as described by McNeilly and Hagen (1974).

Total plasma tryptophan was measured by the method of Wapnir and Stevenson (1969). Plasma was centrifuged in Centriflo membrane cones for 30 min. at 1000 g and a temperature of 4°C, and free plasma tryptophan was measured in the ultrafiltrate as described by Denckla and Dewey (1967) and Wapnir and Stevenson (1969).

In each case the concentrations of oestrone, oestradiol, and free and total plasma tryptophan in the two nights were compared using a t-test for paired observations. Mean concentrations were calculated for each night, and the differences between the mean levels on the two nights determined for each patient. The magnitude of change between the nights in the levels of each hormone, and of free and total plasma tryptophan during the night were plotted for each night, then compared with histograms of sleep stages to show any relationship between changes in plasma levels and sleep stages. The mean levels of the hormones and of free and total tryptophan during each sleep stage were determined, to see whether any sleep stage was associated with either higher or lower levels, and to seek evidence of a diurnal variation the night was divided into

three periods, using 2 a.m. and 5 a.m. as cut-off points, and the mean levels in the three periods of the night compared by analysis of variance.

The relationship between changes in hormone levels and free and total plasma tryptophan were investigated by calculating the correlation coefficient, r , for the levels during each night, and also for the mean nocturnal levels.

RESULTSPATIENTS

A total of 61 patients were interviewed, 36 after referral by their GP and 25 at their own request. Not all of these were suitable, as some did not have symptoms of insomnia, depression, anxiety and hot flushes, some were not willing to give up their previous medication, some had not yet reached the menopause, and some had contraindications to oestrogen treatment. However, 42 were both suitable and willing to take part in the study, though 16 of these had to undergo a six week withdrawal period from their former treatment (four were on oestrogen, four on tranquillisers, six on hypnotics, one on bellergeral, a combination of atropine, ergotamine, and phenobarbitone, and one was receiving an appetite suppressant. From EEG appearances I suspected that one patient in the placebo group had continued regularly to take benzodiazepines during the study, but as her results were unremarkable I have not excluded her.

Although 42 patients started the study, five failed to return after the first night and two dropped out in the first week because of severe side effects (they had continued to take hypnotics until the start of the study, and were consequently suffering withdrawal effects). One patient developed a urinary tract infection in the eighth week of the study, after starting oestrogen treatment, and became very depressed and tearful, and was therefore withdrawn.

A total of 34 patients completed the study, 17 in the oestrone group and 17 in the placebo group. The mean age of the patients in the oestrone group was 49.7 ± 5.7 , while the placebo group patients had a mean age of 48.5 ± 0.9 , and the two groups were similar in the duration of amenorrhoea experienced by their patients (see Table 3).

TABLE 3: Duration of Amenorrhoea (years) of Patients in the Oestrone and Placebo Groups.

Duration of Amenorrhoea (years)	Number of Patients	
	Oestrone Group	Placebo Group
0.25 - 1.0	8	7
1.0 - 3.0	5	7
3.0 - 5.0	1	1
More than 5.0	3	2

SLEEP

1. Subjective Sleep Quality

Both groups showed an improvement in subjective sleep quality as measured by visual analogue scales throughout the study (see Fig. 13), but there was no significant difference between the two groups at any stage, nor was the mean score in either treatment period significantly higher than that in the baseline period in either group.

2. Electrophysiological Recording of Sleep

(a) Sleep Latency

Table 4 shows the group mean sleep latency and the range of the means of individual patients in each period of

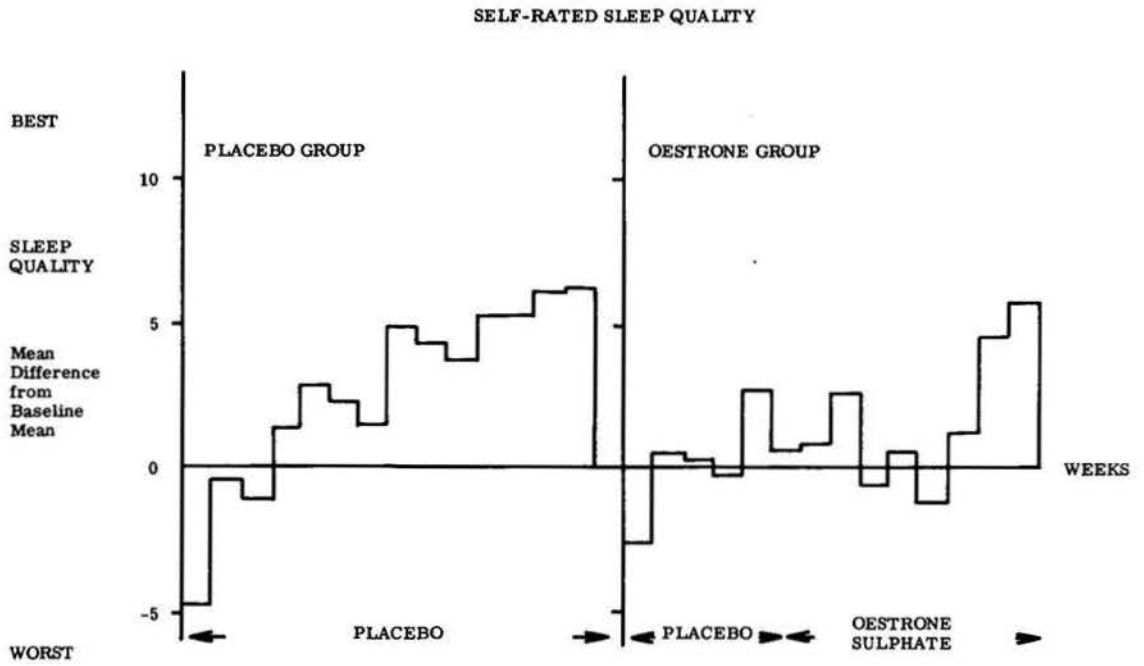


FIG. 13: Visual analogue scale of sleep quality results expressed as the weekly mean difference in millimetres from the baseline mean score in the two groups.

the study for the oestrone and placebo groups. From this it can be seen that the sleep onset latency varied widely between patients in each group, with some patients falling asleep very quickly and others taking as long as one or two hours to fall asleep. The range of sleep latencies was consistently wider in the placebo group than in the oestrone group throughout the study, but despite this there was little difference in the group mean values. Both groups showed a small decrease in the mean sleep latency during the study. The oestrone group showed a mean decrease of 1.5 min. in the first treatment month, and 3.2 min. in the second treatment month, while the placebo group showed mean decreases of 0.2 min. and 7.5 min. It is likely that the decrease in sleep latency experienced by both groups was due to increasing familiarity with the sleep laboratory, and since there was little difference in the changes experienced by the two groups, it seems that oestrogen treatment did not change the length of time patients took to get to sleep.

TABLE 4: Sleep Latency (min) in the Oestrone and Placebo-Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	32.1	30.6	28.9
Range	7.1 - 67.2	2.2 - 76.1	4.5 - 60.3
<u>Placebo Group</u>			
Mean	38.5	38.3	31.0
Range	10.4 - 126.5	8.2 - 108.5	6.5 - 86.1

(b) Sleep Duration

The sleep duration also varied widely in each group, and in the baseline period the mean values of individual patients ranged from less than six hours to almost eight hours. However, the baseline means were very similar, and there was no significant difference between the two groups in the baseline period.

During the study, the sleep duration of both groups increased (see Table 5). In the oestrone group, sleep duration increased significantly from the baseline mean of 423.2 ± 8.2 min to 442.2 ± 7.7 min in the first treatment month ($t = 3.305$, $p < 0.01$) and 446.5 ± 7.2 min in the second treatment month ($t = 2.939$, $p < 0.01$). The increase in the sleep duration of the placebo group from the baseline level of 418.2 ± 7.2 min to 424.3 ± 8.2 min in the first treatment month was short of significance, but the increase from the baseline to the second treatment month level of 429.4 ± 7.2 min was significant ($t = 2.735$, $p < 0.02$). Although the oestrone group showed a greater mean increase than the placebo group in both treatment months, there was no significant difference between the changes in the two groups.

TABLE 5:

TABLE 5: Sleep Duration (min) in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	423.2	442.2	446.5
S.D.	33.9	31.6	29.6
Range	377.1-476.8	370.2-487.1	365.6-478.7
<u>Placebo Group</u>			
Mean	418.2	424.3	429.4
S.D.	29.5	33.9	29.8
Range	342.8-457.7	349.0-472.0	372.8-470.2

(c) Intervening Wakefulness

(i) In the Whole Night. This is a measure of the brokenness of sleep, and may be defined as the amount of time spent awake between periods of sleep. In the baseline period, the patients in the oestrone group had a wider range of mean amounts of intervening wakefulness than those in the placebo group, but again the difference between the means for the two groups in the baseline period is not significant. In both groups the intervening wakefulness decreased throughout the study (see Table 6). In the oestrone group, the intervening wakefulness in the whole night was significantly lower in the first treatment month ($t = 2.888$; $p < 0.02$) and in the second treatment month ($t = 2.689$; $p < 0.02$) than in the baseline period, but in the placebo group these differences were not significant

($t = 1.048$; $t = 0.931$). The oestrone group showed a decrease in intervening wakefulness of 14.4 ± 5.1 min between the baseline period and the first treatment month, and the placebo group a decrease of 4.7 ± 4.5 min, but the difference between the two groups is short of significance ($t = 1.454$). The oestrone group showed a decrease in intervening wakefulness of 15.8 ± 5.9 min between the baseline period and the second treatment month, which is significantly greater than the decrease shown by the placebo group of 2.1 ± 2.2 min ($t = 2.176$, $p < 0.025$).

TABLE 6: Intervening Wakefulness (min) in the Whole Night in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	35.9	21.5	20.1
S.D.	27.8	13.5	15.0
Range	0.0-100.2	0.6-45.7	3.5-44.6
<u>Placebo Group</u>			
Mean	31.5	26.8	29.4
S.D.	18.7	14.6	16.5
Range	4.4-71.8	3.6-57.9	5.4-68.5

(41) Intervening Wakefulness in the First Six Hours of Sleep

To compensate for differences in sleep duration between different subjects and nights, the results may be considered in terms of the first six hours of sleep.

Table 7 shows the mean amounts of intervening wakefulness

in the first six hours of sleep in the oestrone and placebo groups in the three periods of the study, and the results in this table have been obtained by calculating the mean amount of intervening wakefulness in each hour of sleep, then taking the sum of the means for the first six hours. In some cases the sleep duration was less than six hours, and where for example the sixth hour of sleep was complete on three nights, but on the other night there had been only 30 min in this hour, then the mean intervening wakefulness for the sixth hour would be obtained through division by 3.5 instead of 4. This extrapolation was necessary on 22 of the 408 nights recorded. These nights were evenly distributed in the three periods of the study, and 9 occurred in patients in the oestrone group and 13 in the placebo group.

Fig. 14 shows the cumulative intervening wakefulness in the first six hours of sleep in the two groups in the baseline period, first treatment month, and second treatment month, and from this it can be seen that episodes of wakefulness recurred throughout the night in both groups. In the placebo group there was little change in the amount of intervening wakefulness between the three periods, but in the oestrone group the amount of intervening wakefulness decreased throughout the night when the patients received oestrogen treatment. The mean values and range of results are given in Table 7, and it can be seen from this that the mean amount of intervening wakefulness was higher and the range wider in the group of patients who later received

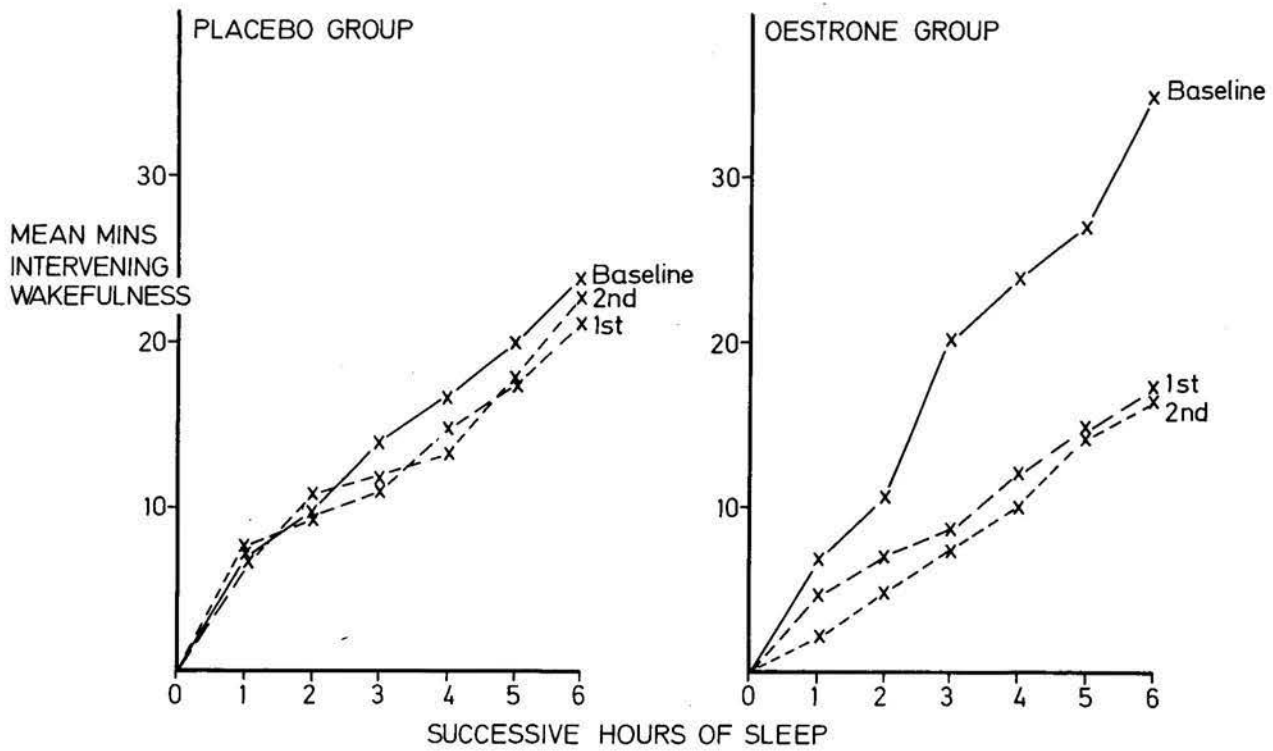


FIG. 14: Mean cumulative intervening wakefulness (min) in the first six hours of sleep in the oestrone and placebo groups during the baseline period, first treatment month, and second treatment month.

oestrogen than in the placebo group in the baseline period, but although the difference between the groups was large, it was not statistically significant ($t = 1.140$). The mean intervening wakefulness in the first six hours of sleep in the oestrone group was significantly lower in the first treatment month ($t = 2.624$, $p < 0.02$) and the second treatment month ($t = 2.460$, $p < 0.02$) than in the baseline period, but in the placebo group these differences were not significant ($t = 0.569$, $t = 0.422$).

TABLE 7: Intervening Wakefulness (min) in the First Six Hours of Sleep in the Oestrone Group and Placebo Group in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	34.6	17.3	16.6
S.D.	32.6	12.9	13.9
Range	0 -122.8	0 -41.2	0.9-44.5
<u>Placebo Group</u>			
Mean	24.0	21.4	23.0
S.D.	19.6	14.3	18.1
Range	1.6-69.7	2.0-40.4	1.9-56.9

When we compare the changes in intervening wakefulness in the first six hours of sleep between the periods of the study, the oestrone group showed a decrease of 17.3 ± 6.6 min, and the placebo group a decrease of 2.6 ± 4.6 min between the baseline period and the first treatment month. The difference between the two groups was significant

($t = 1.816$, $p < 0.05$). Comparing the baseline period and the second treatment month, the oestrone group showed a decrease of 18.0 ± 7.3 min, and the placebo group a decrease of 1.0 ± 2.4 min, and the difference between the two groups was again significant ($t = 2.205$, $p < 0.025$).

It is unlikely that the difference between the groups is due to the extrapolations where patients slept for less than six hours, since the proportion of nights in which this extrapolation was needed is small, and it can be seen from Fig. 14 that the results would have been the same if we had considered only the first four hours of sleep, which did not include any extrapolated results.

(d) Number of Arousals to Wakefulness

(i) In the Whole Night. The brokenness of sleep may also be measured in terms of the number of episodes of wakefulness during the night. Table 8 shows the group mean, standard deviation, and the range of results of the number of arousals in the patients of the two groups in the three periods of the study. In the baseline period, the patients in the oestrone group had a higher mean number of wakenings than those of the placebo group, but again the difference was not significant.

The number of arousals to wakefulness increased slightly above baseline levels in the first treatment month in both groups. In the oestrone group the mean increase was 0.1 ± 0.4 , and in the placebo group was 0.3 ± 0.4 , but this increase was not significant in either

case (oestrone group, $t = 0.129$; placebo group, $t = 0.799$) nor was the difference between the groups significant ($t = 0.470$).

In the second treatment month both groups had fewer arousals than in the baseline period, the difference being significant in the case of the oestrone group ($t = 2.212$, $p < 0.025$) but not in the placebo group ($t = 0.276$).

The oestrone group had a decrease in arousals of 0.9 ± 0.4 in this period compared with an increase of 0.1 ± 0.4 in the placebo group, and the difference between the two groups is significant ($t = 1.717$, $p < 0.05$).

TABLE 8: Number of Arousals to Wakefulness in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	5.9	6.0	5.0
S.D.	4.3	4.7	3.5
Range	0 -14.5	0.3-14.3	0.8-12.5
<u>Placebo Group</u>			
Mean	5.3	5.6	5.4
S.D.	2.5	3.0	3.1
Range	1.8-11.8	2.3-11.8	2.0-11.8

(ii) Arousals to Wakefulness in the First Six Hours Sleep

It is possible that most of the awakenings take place either at the beginning of the night or in the last hour of sleep, as morning approaches, and to investigate this the number of arousals to wakefulness per hour in the first six hours of sleep have been calculated. Fig. 15 shows the cumulative arousals to wakefulness in the first six hours of sleep in the two groups in the three phases of the study, and it can be seen from this that wakenings recur throughout the night, and are not restricted to either the beginning or the end of the sleep period. In the placebo group there is little difference in the frequency of arousals in the three periods of the study, but the oestrone group show a decrease in the number of arousals to wakefulness in the second treatment month.

Table 9 shows the mean number of arousals to wakefulness in the first six hours of sleep in the two groups in the baseline period, first treatment month, and second treatment month. Both groups showed a slight increase in wakenings in the first six hours sleep in the first treatment month, but this increase was not significant in either group, nor was there any significant difference between the two groups. In the second treatment month, the oestrone group showed a significant decrease below the baseline level ($t = 2.336$, $p < 0.025$) while the placebo group showed a slight increase ($t = 0.59$, N.S.). The decrease in the number of awakenings between the baseline period and the second treatment month in the oestrone group

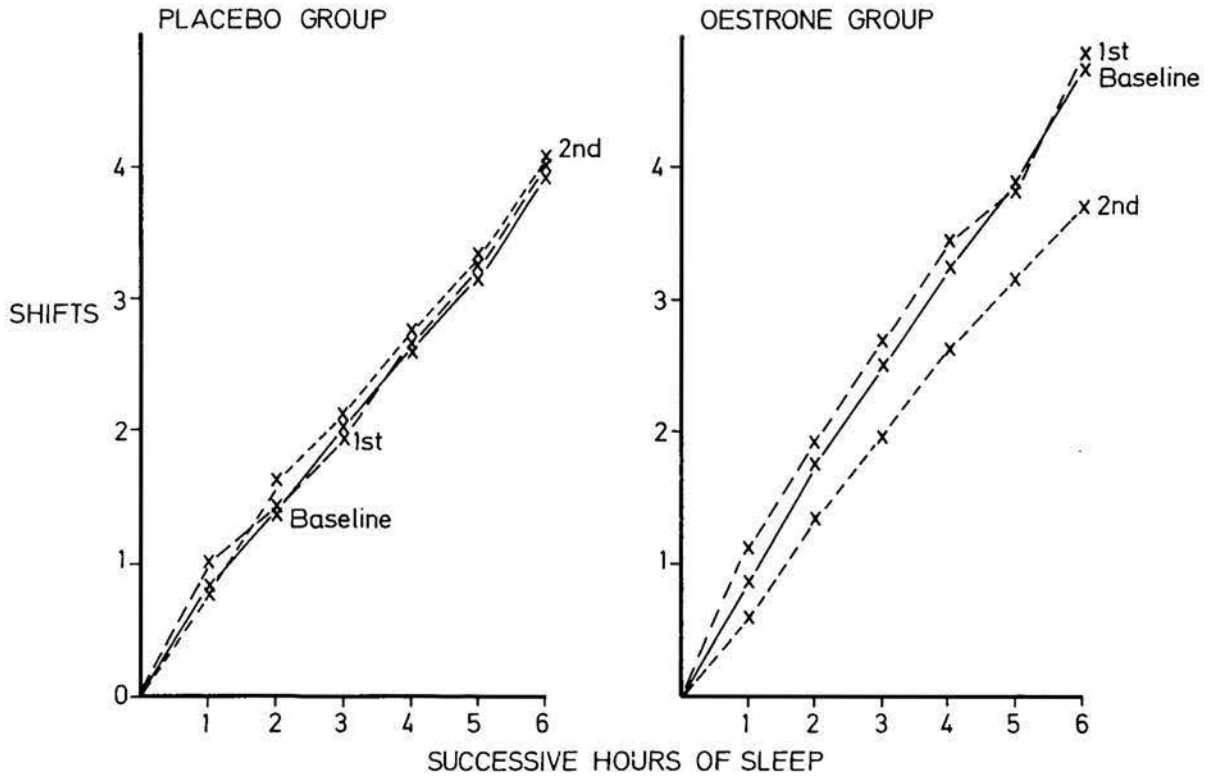


FIG. 15: Cumulative mean number of awakenings in the first six hours of sleep in the oestrone and placebo groups in the baseline period, first treatment month, and second treatment month.

was 1.05 ± 0.45 , and this is significant when compared with the increase of 0.18 ± 0.31 in the placebo group ($t = 2.260$, $p < 0.025$).

TABLE 9: Number of Arousals to Wakefulness in the First Six Hours of Sleep in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	4.8	4.9	3.7
S.D.	3.8	3.9	2.8
Range	0-13.0	0-12.0	0.3-8.8
<u>Placebo Group</u>			
Mean	3.9	4.1	4.1
S.D.	2.5	2.5	2.9
Range	0.5-10.0	1.5-9.0	1.3-9.5

(e) Stage 1 Sleep

The mean amounts of stage 1 sleep in the whole night and in the first six hours of sleep in the oestrone and placebo groups in the three periods of the study are shown in Table 10. Neither group showed any significant change in the amount of stage 1 sleep, nor were there any significant differences between the two groups either in terms of the amount of this stage, or in the changes between the baseline and treatment periods, in either the whole night or in the first six hours of sleep. Since the amount of stage 1 sleep also fell slightly in the treatment periods,

the decrease in the amount of intervening wakefulness in the oestrone group in the active treatment periods cannot have been due to an increase in drowsiness.

TABLE 10: Amount of Stage 1 Sleep (min) in the Whole Night and First Six Hours of Sleep in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Total	34.0 \pm 2.3	34.3 \pm 3.1	31.2 \pm 2.8
In the 1st Six Hours Sleep	28.6 \pm 2.6	27.2 \pm 2.7	24.9 \pm 2.6
<u>Placebo Group</u>			
Total	40.0 \pm 3.1	36.7 \pm 3.3	37.9 \pm 3.3
In the 1st Six Hours Sleep	33.3 \pm 2.6	27.9 \pm 2.1	30.6 \pm 2.6

The number of shifts to stage 1 sleep are shown in Table 11, and from this it can be seen that the number of arousals to stage 1 was greater in the oestrone group in the first treatment month than in the baseline period, but fell again to baseline level in the second treatment month. The placebo group had a fall in the number of shifts to stage 1 in the first treatment month, but the levels in the second treatment month were the same as those of the baseline period. The number of shifts to stage 1 in the whole night was increased in the oestrone group by 3.5 ± 1.7 , and decreased in the placebo group by 2.2 ± 1.5 in the first treatment month, and the difference between the two

groups is significant ($t = 2.441$, $p < 0.025$). However, in the second treatment month, these changes are reversed, so that the oestrone group have 0.5 ± 1.7 and the placebo group 0.1 ± 1.5 fewer shifts to stage 1 than in the baseline period, and the difference between the two groups is not significant ($t = 0.200$).

When considered in terms of the first six hours of sleep, the difference between the two groups is much less (see Table 11). In the first treatment month, the oestrone group shows an increase of 1.7 ± 1.7 and the placebo group a decrease of 2.3 ± 1.5 shifts to stage 1 in the first six hours sleep, but this difference is short of significance. ($t = 1.788$). In the second treatment month, the means were similar to baseline levels in both groups, with the oestrone group showing a decrease of 1.4 ± 1.8 and the placebo group a decrease of 0.3 ± 1.2 shifts, and there was again no significant difference between the two groups ($t = 0.497$).

Since the increase in the number of shifts to stage 1 sleep shown in the first treatment month by the oestrone group is considerably greater in the whole night than in the first six hours of sleep, it may be due to an increase in the number of arousals in the later part of the night, associated with an increase in sleep duration. However, this does not entirely account for the increase, and when the results are analysed in terms of hours of sleep, an increase in the number of shifts to stage 1 can be seen in the third and fourth hours of sleep.

TABLE 11: Number of Shifts to Stage 1 Sleep in the Whole Night and First Six Hours of Sleep in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Total	31.7 \pm 2.2	35.2 \pm 3.3	31.2 \pm 2.4
In 1st Six Hours Sleep	27.1 \pm 2.5	28.8 \pm 3.3	25.7 \pm 2.3
<u>Placebo Group</u>			
Total	35.2 \pm 2.4	33.0 \pm 2.5	35.1 \pm 2.2
In 1st Six Hours Sleep	30.2 \pm 1.9	27.9 \pm 2.0	29.9 \pm 2.0

(f) Stage 2 Sleep

Both groups showed an increase in stage 2 sleep throughout the study (see Table 12). In the case of the oestrone group the total amount of stage 2 sleep increased significantly from the baseline level of 215.4 \pm 6.7 min to 230.0 \pm 6.9 min in the first treatment month ($t = 2.821$, $p < 0.02$) and to 232.1 \pm 6.7 min in the second treatment month ($t = 2.704$, $p < 0.02$). The changes in the placebo group between the three periods of the study were not significant. Although the oestrone group showed a greater mean increase in the amount of stage 2 sleep than the placebo group, the difference between the two groups was not significant.

The changes in the amount of stage 2 sleep are related to changes in sleep duration, as when the results are considered in terms of the first six hours of sleep, there

are no significant differences between the three phases of the experiment in either group (see Table 12).

TABLE 12: Amount of Stage 2 Sleep (min) in the Whole Night and First Six Hours of Sleep in the Oestrone and Placebo Groups in the Three Periods of the Study

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Total	215.4 \pm 6.7	230.0 \pm 6.9	232.1 \pm 6.7
In 1st Six Hours Sleep	182.7 \pm 5.5	188.2 \pm 7.1	188.0 \pm 5.5
<u>Placebo Group</u>			
Total	209.4 \pm 7.4	210.8 \pm 8.1	217.6 \pm 7.7
In 1st Six Hours Sleep	179.6 \pm 5.5	179.2 \pm 6.3	180.7 \pm 5.0

The mean number of shifts to stage 2 sleep in the whole night increased in the first treatment month in the oestrone group and decreased in the placebo group, but was similar to the baseline level in both groups in the second treatment month (see Table 13). When the changes between the baseline period and the first treatment month were compared, the oestrone group showed an increase of 3.9 ± 2.1 in the number of shifts to stage 2 and the placebo group a decrease of 2.4 ± 1.6 , and the difference between the groups was significant ($t = 2.436$, $p < 0.025$). Between the baseline and the second treatment month, the number of shifts increased by 0.8 ± 2.0 in the oestrone group and showed no mean change (0.0 ± 1.7) in the placebo group, and there was no significant difference between the two groups

($t = 0.30$). There was no significant difference between the mean number of shifts in the three periods of the study in either group.

When considered in terms of the first six hours of sleep, there were no significant changes either between the groups or between the three periods of the study. The increase in the number of shifts to stage 2 sleep in the oestrone group is much smaller when considered in the first six hours of sleep than the whole night, which suggests that much of the increase is due to the patients having more stage 2 in a longer night's sleep on oestrone.

TABLE 13: Number of Shifts to Stage 2 Sleep in the Whole Night and First Six Hours of Sleep in the Oestrone and Placebo Groups in the Three Periods of the Study.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Total	40.2 \pm 2.1	44.1 \pm 3.1	41.0 \pm 2.5
In 1st Six Hours Sleep	34.3 \pm 2.2	36.9 \pm 3.1	34.3 \pm 2.4
<u>Placebo Group</u>			
Total	44.7 \pm 7.2	42.3 \pm 2.4	44.7 \pm 2.6
In 1st Six Hours Sleep	38.7 \pm 1.8	36.6 \pm 1.8	38.6 \pm 2.4

(g) Slow Wave Sleep

There was considerable variation in the amount of slow wave sleep in the subjects of the two groups. In the oestrone group, the mean amount of slow wave sleep ranged from 13.6 min to 103.6 min, and in the placebo group from 38.5 min to 119.7 min, but despite this, the baseline means of the two groups were very similar (see Table 14). Since slow wave sleep occurs predominantly in the first part of the night, the amount of slow wave sleep in the first six hours of sleep is almost identical to that in the whole night.

There were no significant changes in either the total amount of slow wave sleep, or in slow wave sleep in the first six hours of sleep throughout the study, nor were there any significant differences between the changes experienced by the two groups. There were no changes in the number of shifts to stages 3 + 4 in the whole night or in the first six hours of sleep in either the oestrone or placebo groups.

TABLE 14: Amount of Slow Wave Sleep (min) in the Whole Night and the First Six Hours of Sleep in the Oestrone and Placebo Groups in the Three Periods of the Study.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Total	60.4 \pm 6.9	58.9 \pm 7.6	57.7 \pm 6.0
In 1st Six Hours Sleep	58.8 \pm 6.3	55.9 \pm 7.1	56.1 \pm 5.7
<u>Placebo Group</u>			
Total	65.4 \pm 5.0	70.5 \pm 6.1	68.3 \pm 5.6
In 1st Six Hours Sleep	63.7 \pm 4.4	68.4 \pm 5.8	66.8 \pm 5.3

(h) REM Sleep

As can be seen from Table 15, the oestrone group had a higher mean amount of REM sleep in the baseline period than the placebo group, but this difference was not significant ($t = 1.51$). Both groups showed an increase in REM sleep throughout the study, but this increase was not significant in either treatment month in the placebo group, or in the oestrone group in the first treatment month. However, in the oestrone group the increase from the baseline level of 113.5 min to 126.9 min in the second treatment month was significant ($t = 2.577$, $p < 0.02$).

In both treatment periods the oestrone group showed a greater increase in REM sleep than the placebo group. In the first treatment month, the oestrone group showed an increase of 5.6 ± 3.1 min above baseline levels, and the placebo group an increase of 3.4 ± 2.9 min, but the difference between the two groups was not significant ($t = 0.530$). The difference was significant when comparing the baseline and the second treatment month, when the oestrone group showed an increase of 13.3 ± 4.7 min and the placebo group an increase of 2.3 ± 2.0 min ($t = 2.184$, $p < 0.05$).

When considered in terms of the first six hours sleep, there was little change in the amount of REM sleep in either group (see Table 15), suggesting that the changes during the whole night are related to changes in sleep duration.

There were no significant changes in the number of shifts to REM sleep in either group in the whole night or

in the first six hours sleep, and no significant difference between the changes in the two groups.

TABLE 15: Amount of REM Sleep (min) in the Whole Night and First Six Hours of Sleep in the Oestrone and Placebo Groups in the Three Periods of the Study.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Total	113.5 \pm 5.7	119.1 \pm 5.5	126.8 \pm 5.5
In 1st Six Hours Sleep	89.3 \pm 3.6	88.7 \pm 3.9	91.3 \pm 3.3
<u>Placebo Group</u>			
Total	103.4 \pm 3.5	106.8 \pm 4.1	105.7 \pm 3.1
In 1st Six Hours Sleep	82.9 \pm 2.7	84.0 \pm 3.1	81.5 \pm 1.8

(1) REM Onset Latency

There was little change in REM onset latency in either group, as can be seen from Table 16, and there was no significant difference in the changes experienced by the two groups.

TABLE 16: REM Onset Latency (min) in the Oestrone and Placebo Groups in the Baseline Period, First Treatment Month, and Second Treatment Month.

	Baseline	1st Treatment Month	2nd Treatment Month
<u>Oestrone Group</u>			
Mean	88.3	80.4	81.1
Range	54.9 \pm 140.4	52.5 \pm 147.3	59.6 \pm 137.0
<u>Placebo Group</u>			
Mean	87.7	86.4	86.3
Range	64.3 \pm 116.2	60.6 \pm 129.8	54.1 \pm 153.8

MOOD

Both groups showed an improvement in mood as measured by both the Hamilton depression rating scale (see Fig. 16) and the visual analogue scale of depression (see Fig. 17), but neither scale showed a significant difference between the oestrone and placebo groups.

At the start of the study the Hamilton depression score of the oestrone group was 16.3 ± 1.9 , and of the placebo group was 18.2 ± 2.0 , indicating depression of only moderate severity in both groups. As can be seen from Fig. 16, the Hamilton depression score fell markedly in the baseline period in both groups, to a mean of 7.9 ± 1.2 in the oestrone group and 10.1 ± 1.5 in the placebo group. These scores indicate only mild depression, and are so low that they leave little scope for improvement in the active treatment period. The Hamilton depression score of the oestrone group fell to 7.3 ± 1.3 at the end of the first treatment month, and 5.9 ± 1.8 at the end of the second treatment month, while the placebo group scores fell to 6.2 ± 1.3 and 4.5 ± 0.7 respectively.

In both groups the difference between the Hamilton depression scores at the beginning and end of the baseline period is significant (oestrone group $t = 4.465$, $p < 0.001$; placebo group $t = 6.125$, $p < 0.001$). The placebo group also showed a significant decrease in the score from the end of the baseline period to the end of the first treatment month ($t = 2.810$, $p < 0.02$) and to the end of the second treatment month ($t = 3.301$, $p < 0.01$) but in the oestrone

group these changes were not significant ($t = 0.997$ and $t = 1.552$). There was however no significant difference between the groups when the changes in score of the two groups are compared.

The visual analogue scale of depression showed little difference between the baseline period and the two treatment months in either group. The mean score of the oestrone group was 47.1 ± 1.9 in the baseline period, 47.9 ± 2.3 in the first treatment month, and 49.1 ± 3.0 in the second treatment month, while the scores of the placebo group were 47.6 ± 2.2 , 50.5 ± 1.9 , and 52.4 ± 3.4 respectively. There was no significant difference between the three periods of the study in either group, nor between the changes in score of the groups.

Fig. 17 shows the weekly mean scores of the two groups expressed as difference from the baseline mean. This shows a gradual improvement in mood in both groups, similar to the changes shown by the Hamilton depression rating scale. There was a significant negative correlation between the Hamilton depression rating scale score and the visual analogue scale score at the start of the study, and at weeks 10 and 14 ($r = -0.53$, -0.45 , and -0.49 ; $p < 0.01$), but not at week 6 ($r = -0.10$; N.S.). There was also a significant negative correlation between the change in scores on the two scales between the end of the baseline period and the end of the first treatment month ($r = -0.34$, $p < 0.05$) and between the end of the first treatment month and the end of the study ($r = -0.38$, $p < 0.05$), but when the

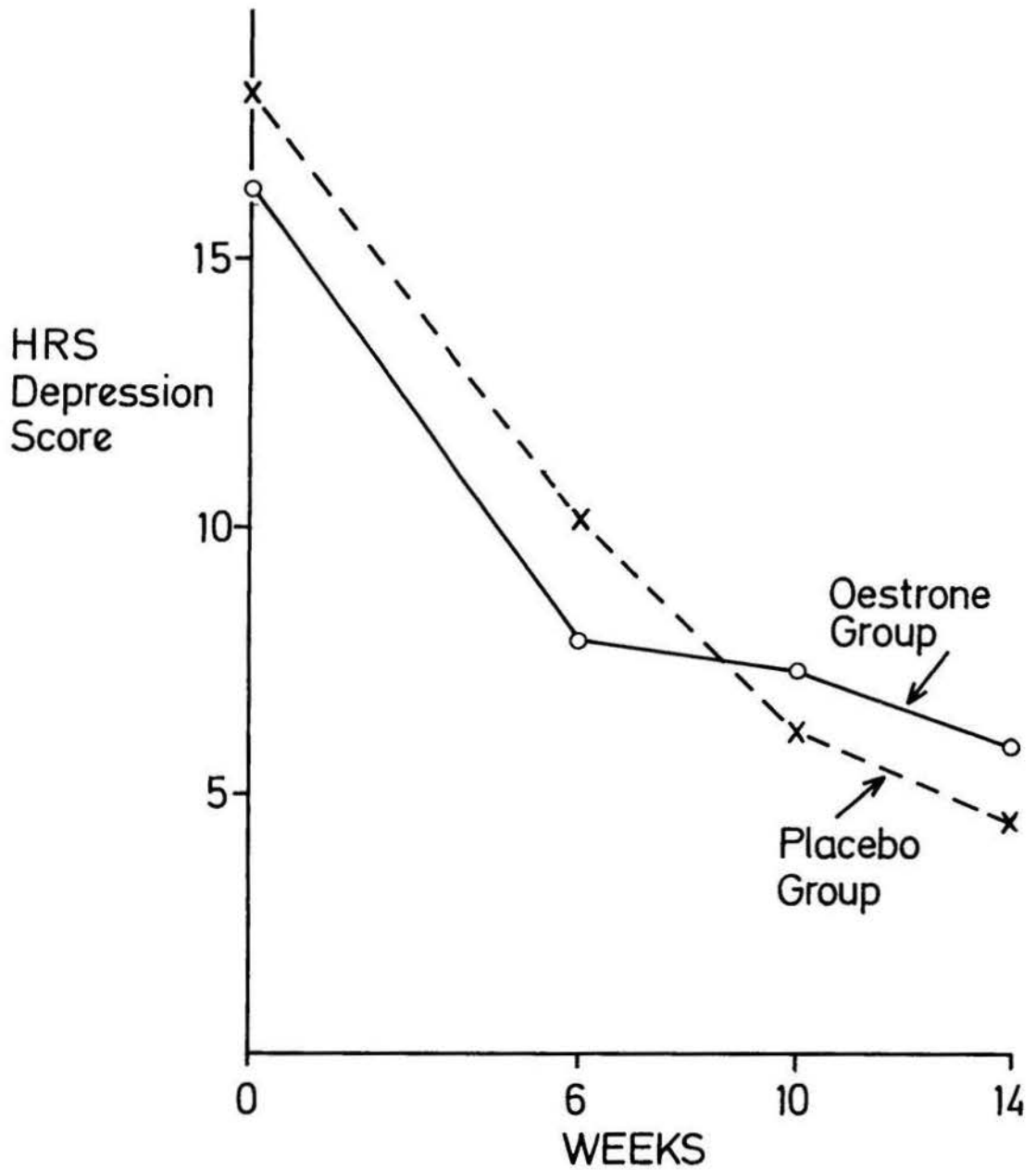


FIG. 16: Mean Hamilton depression rating scale scores of the oestrone and placebo groups.

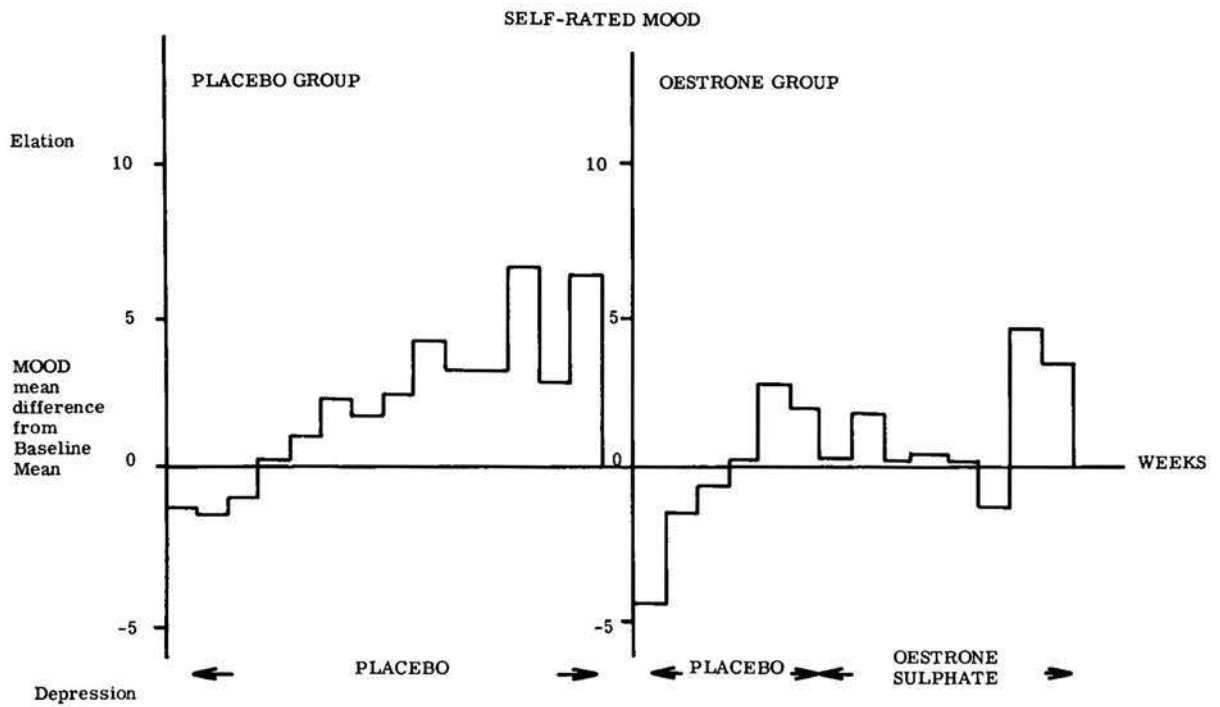


FIG. 17: Visual analogue scale of mood results expressed as the weekly mean difference in millimetres from the baseline mean score in the oestrone and placebo groups.

changes between the start and end of the baseline period were considered, the correlation was short of significance ($r = -0.33$). The correlations are negative because improvement is shown on the Hamilton rating scale by a fall in the score and on the visual analogue scale by an increase in the score.

ANXIETY

Both oestrone and placebo groups showed a steady decrease in their anxiety levels throughout the study. This parallels the improvement in depression, as can be seen by comparing Figs. 16 and 18, which show the results of the Hamilton depression and anxiety scales, and Figs. 17 and 19, which show the visual analogue scale results.

In both groups, the Hamilton anxiety scale showed a marked improvement in the score in the baseline period, with a further improvement in the two treatment months. The score of the oestrone group fell from 17.2 ± 1.8 at the start of the study to 9.7 ± 1.3 at the end of the baseline period, 7.7 ± 1.2 at the end of the first treatment month, and 5.6 ± 1.4 at the end of the second treatment month. Over the same period, the score of the placebo group fell from 20.1 ± 2.1 to 11.4 ± 1.3 , to 6.5 ± 1.1 , and to 5.4 ± 0.7 at the end of the study.

In both groups the difference between the score at the start of the study and the end of the baseline period is significant (oestrone group $t = 5.455$, $p < 0.001$; placebo group $t = 5.606$, $p < 0.001$). The decrease from the end of

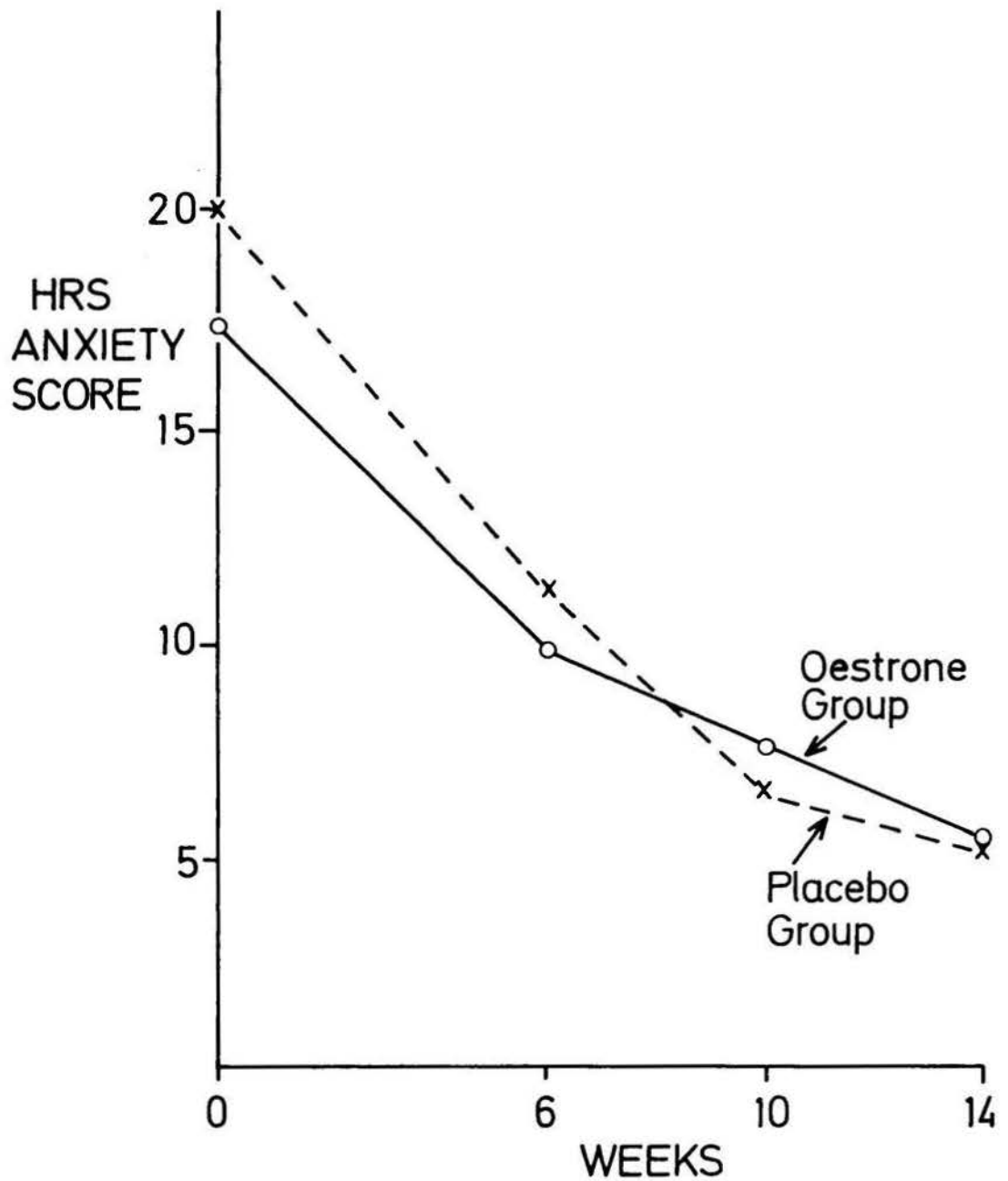


FIG. 18: Mean Hamilton anxiety rating scale scores of the oestrone and placebo groups.

the baseline period to the end of the first treatment group is significant for the placebo group ($t = 4.363$, $p < 0.001$) but not for the oestrone group ($t = 1.748$) but the decrease from the end of the baseline period to the end of the study is significant in both groups (oestrone group, $t = 3.442$, $p < 0.01$; placebo group, $t = 4.348$, $p < 0.001$). Although the placebo group showed a greater change in score than the oestrone group, the difference between the groups was not significant.

Visual analogue scale scores showed a similar pattern of improvement, as can be seen from Fig. 19, but failed to show significant differences between the three phases of the study or between the changes in score of the two groups. The baseline mean score of the oestrone group was 47.1 ± 1.7 , increasing to 47.9 ± 1.7 in the first treatment month and 48.7 ± 2.2 in the second treatment month. The score of the placebo group was 47.4 ± 1.9 in the baseline period, 49.8 ± 1.9 in the first treatment month, and 51.5 ± 3.0 in the second treatment month. On this rating scale a high score indicates calm, a low score anxiety.

There was no significant correlation between the Hamilton anxiety rating scale score and the visual analogue scale of anxiety score, nor between the changes in score on the two scales.

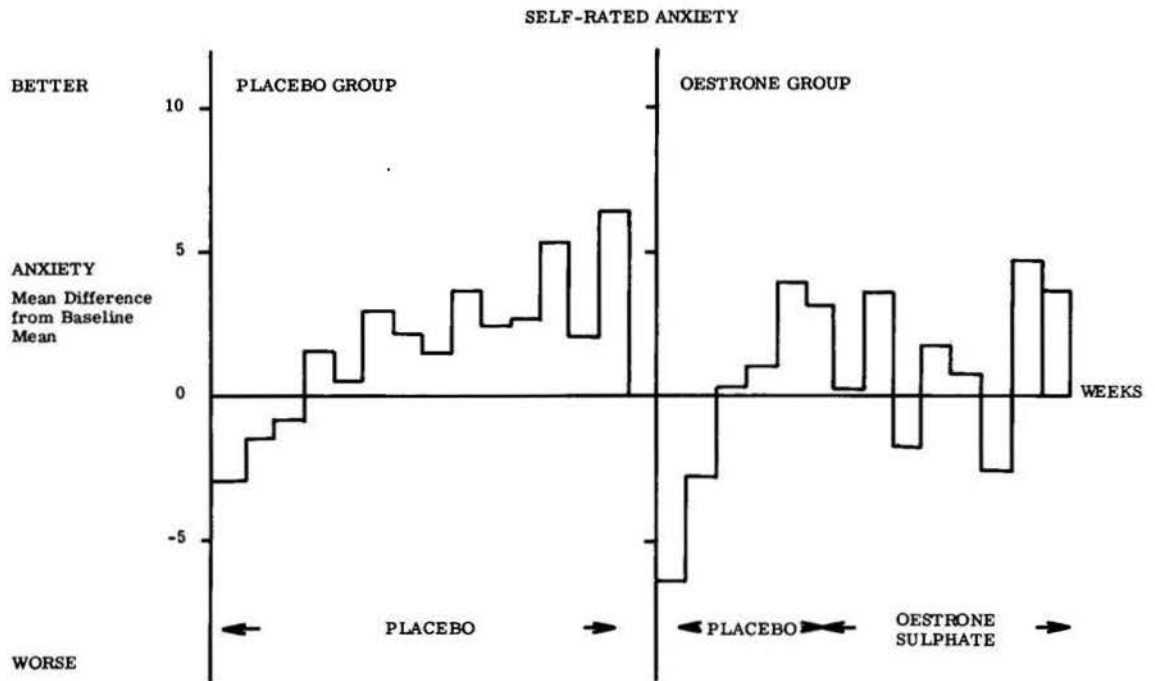


FIG. 19: Visual analogue scale of anxiety results expressed as the weekly mean difference in millimetres from the baseline mean score in the oestrone and placebo groups.

HOT FLUSHES

The number of hot flushes experienced by the patients varied widely. Two patients in the oestrone group and one in the placebo group experienced no hot flushes at all during the study, and one in each group complained that her hot flushes were so frequent that she could not keep count of them. The maximum recorded in one day was 12, but most of the patients had only one or two hot flushes, and since the daily mean was so low, the results are expressed as the weekly total. In the oestrone group the weekly total of hot flushes ranged from 0 to 67, and in the placebo group from 0 to 72.

The number of hot flushes experienced by each group fell during the study, as can be seen from Fig. 20. The placebo group had a higher mean hot flush count than the oestrone group throughout the study, but there was little difference in the rate of fall in the hot flush count in the two groups. In the baseline period, the mean weekly hot flush count of the oestrone group was 11.8 ± 3.4 and this fell to 6.7 ± 1.7 in the first treatment month, and 6.5 ± 2.0 in the second treatment month. Although the hot flush count fell, it was not significantly lower in the active treatment period than in the baseline, and it can be seen from Fig. 20 that the greatest fall in the number of hot flushes occurred in the baseline period, and there was little further change after the start of oestrogen treatment. In the placebo group, the mean

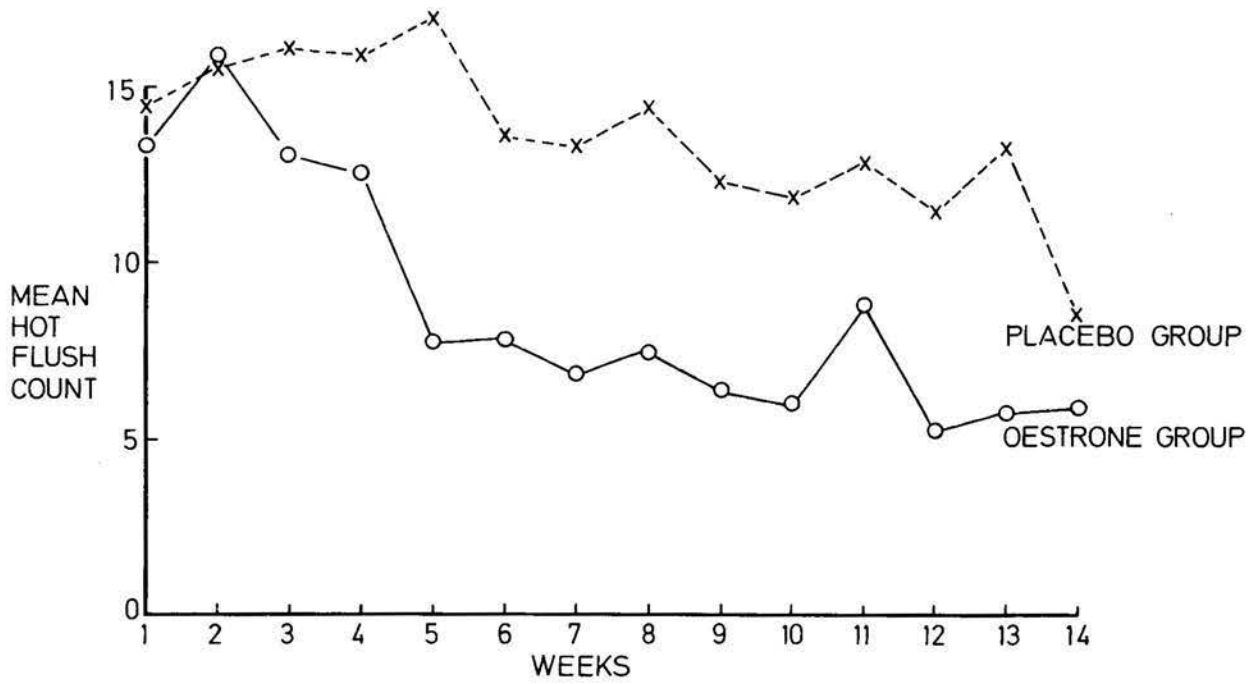


FIG. 20: Mean weekly hot flush count of the oestrone and placebo groups.

weekly hot flush count in the baseline period was 15.4 ± 4.4 and although this is higher than the baseline mean of the oestrone group the difference between the groups was not significant ($t = 0.67$). The weekly hot flush count of the placebo group fell to 13.2 ± 3.4 in the first treatment month and 10.8 ± 3.5 in the second treatment month, but these levels are not significantly lower than the baseline mean.

The oestrone group showed a slightly greater fall in the hot flush count than the placebo group, but the difference between the groups was not significant. Between the baseline period and the first treatment month, the oestrone group showed a mean decrease of 5.1 ± 3.1 hot flushes per week, and the placebo group a mean decrease of 2.2 ± 1.8 hot flushes ($t = 0.83$, N.S.), and between the baseline and second treatment month the hot flush count of the oestrone group fell by 5.3 ± 3.3 , compared with a fall of 4.6 ± 2.6 in the placebo group ($t = 0.171$, N.S.).

The patients also rated the severity of their hot flushes on a visual analogue scale, and only one patient in the placebo group failed to complete this rating. The results are shown in Fig. 21, which shows the difference of the mean weekly score from the baseline mean for each week of the study in each group. From this it can be seen that the hot flush severity fell during the study in both groups.

The mean baseline score of the oestrone group was 19.1 ± 4.1 , and although this is lower than that of the

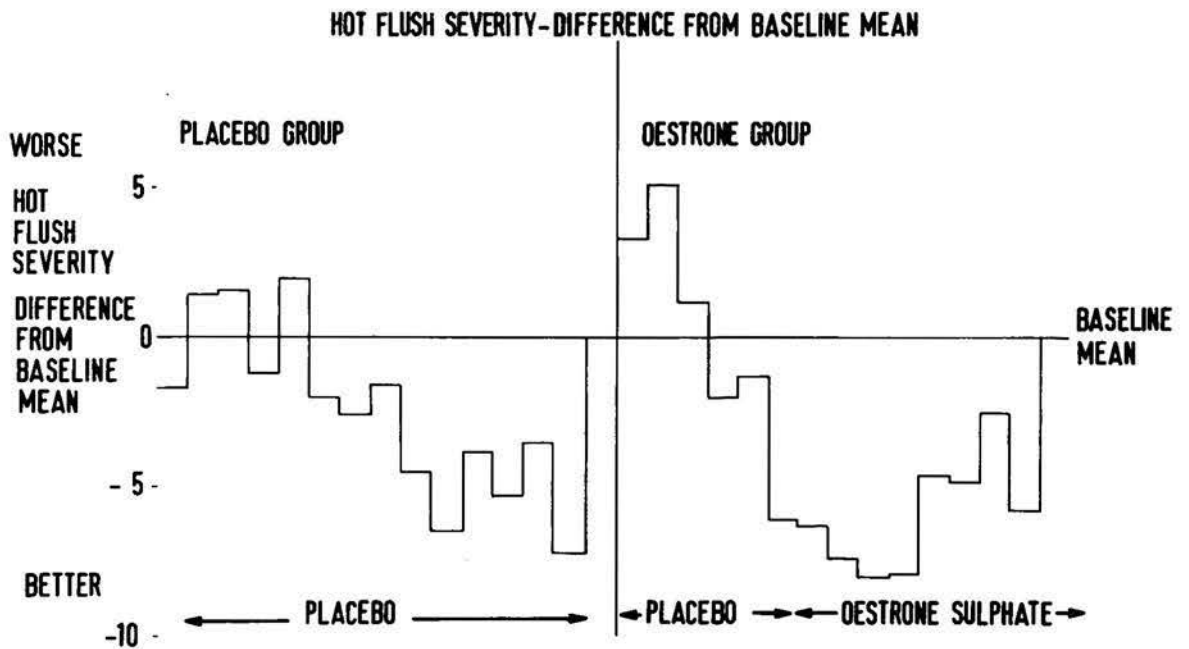


FIG. 21: Hot flush severity rating expressed as the weekly mean difference in millimetres from the baseline mean in the oestrone and placebo groups.

placebo group, 26.0 ± 5.1 , the difference between the two groups was not significant ($t = 1.06$). The mean score of the oestrone group was 12.1 ± 3.0 in the first treatment month, and 12.1 ± 3.3 in the second treatment month, and both of these are significantly lower than the baseline mean (first month, $t = 2.32$, $p < 0.025$; second month, $t = 1.79$, $p < 0.05$). However, inspection of Fig. 21 shows that the fall in score occurred mainly in the baseline period, and there was little change in the score after the start of active treatment.

In the placebo group, the mean score in the first treatment month, 19.8 ± 4.3 , was not significantly lower than the baseline mean ($t = 1.71$) but in the second treatment month there was a further fall in the score to 18.4 ± 5.2 , and this is significantly lower than the baseline mean ($t = 2.00$, $p < 0.05$).

The magnitude of the change in score was similar in the two groups, and there was no significant difference between them. Between the baseline period and the first treatment month the score of the oestrone group fell by 7.0 ± 2.8 , and the placebo group by 6.2 ± 3.6 ($t = 0.390$, N.S.), and between the baseline and second treatment month the score of the oestrone group fell by 7.0 ± 3.8 , compared with 7.6 ± 3.8 in the placebo group ($t = 0.120$, N.S.).

The hot flush severity scale shows a similar pattern of change to that shown by the hot flush count, as can be seen by comparing Figs. 20 and 21. There was a significant positive correlation between the daily hot flush count

and the severity rating for that day in all cases. Obviously, where the patient had no hot flushes the severity was also rated as 0, so in cases with no hot flushes the correlation was absolute, but in the other cases the correlation coefficient r ranged from 0.54 to 0.95 ($p < 0.001$ in all cases).

There was no significant correlation between the mean hot flush count or hot flush severity score and the mean total intervening wakefulness or sleep duration in the three periods of the study, nor was there any correlation between the changes in the hot flush count or hot flush severity score and changes in either intervening wakefulness or sleep duration.

NEUROENDOCRINE STUDIES

Blood studies were carried out on twelve patients, six in the placebo group and six in the oestrone group. For these investigations, the patients attended the sleep laboratory on two extra nights, one in the baseline period in week four and one at the end of the first treatment month. Blood study nights were carried out either three or four nights before the next routine recording night, to avoid influencing the results of the sleep study. Only four of the patients in the oestrone group completed the second blood night, since it proved impossible to cannulate a vein on that night in one patient, and a second patient dropped out half way through the study because of a urinary tract infection. Table 17 shows the age of patients

undergoing blood studies, and the duration of amenorrhoea before the start of the study.

TABLE 17: Age and Duration of Amenorrhoea in Patients in Neuroendocrine Study.

Case No.	Age	Duration of Amenorrhoea (years)
<u>Placebo Group</u>		
1	48	0.3
2	51	2.0
3	53	7.0
4	52	5.0
5	45	0.3
6	49	2.0
<u>Oestrone Group</u>		
7	51	1.5
8	56	8.0
9	44	0.5
10	50	0.3
11	49	4.0
12	56	8.0

Sleep Results

As was predicted, patients did not sleep so well on blood study nights as on normal recording nights, because of the stress of having an intravenous cannula inserted and of sleeping with it taped in place. Table 18 shows the mean values of sleep latency, sleep duration, and amount of the sleep stages for each blood night, and also for the last night recorded before each blood night, and

it will be seen from this table that sleep duration was shorter on the blood nights than the preceding night, and the amount of intervening wakefulness and stage 1 sleep was greater. The difference in sleep duration was not significant, but there was significantly more stage 1 sleep in the first blood night than the preceding night ($t = 2.160$, $p < 0.025$) and in the second blood night there was significantly more intervening wakefulness ($t = 1.828$, $p < 0.05$) and less stage 2 sleep ($t = 1.948$, $p < 0.05$) than in the preceding night. Slow wave sleep and REM sleep were unchanged.

TABLE 18: Sleep Onset Latency, Duration, and the Amount of each Sleep Stage (min) on the two Blood Nights and the Preceding Night.

Sleep Stage	Blood Night 1	Preceding Night	Blood Night 2	Preceding Night
Sleep Latency	30.0	26.6	22.0	30.5
Sleep Duration	420.9	427.9	410.5	439.9
Intervening Wakefulness	35.7	23.8	35.1	15.7
Total Stage 1	53.2	39.6	42.0	35.6
Total Stage 2	216.3	236.8	192.7	220.2
Slow Wave Sleep	51.4	51.8	71.5	62.2
Total REM Sleep	99.9	99.4	104.3	115.3

OESTROGEN LEVELSOestrone

In all cases, both oestrone and oestradiol levels showed episodic variation throughout the night. The levels varied widely and rapidly, and this variation persisted even when the patient was on oestrogen treatment, as can be seen from Fig. 22, which shows the oestrone levels during nights 1 and 2 in Case 10, a patient who received oestrogen treatment in the second part of the study.

There was considerable variation in the mean oestrone levels between patients, as can be seen from Table 19, but in most cases the mean level was within the range expected in the early menstrual cycle. In some patients in the placebo group there was a surprisingly large difference between the mean oestrone levels on the first and second blood nights, e.g. Case 1 showed an increase of 293.6 pmol/l (7.9 ng/dl) and Case 5 a decrease of 170.1 pmol/l (4.6 ng/dl), but when the levels of the two nights were compared in each case, using a t-test for paired observations, this change was significant only in Case 5 ($t = 2.830$, $p < 0.01$).

The patients in the oestrone group showed an increase in their mean oestrone levels on the second blood night, as would be expected after four weeks treatment with piperazine oestrone sulphate, but the magnitude of the change varied considerably between patients. Case 9 showed only a small increase, of 81.5 pmol/l (2.2 ng/dl), but the remaining three patients showed a marked increase, of 483.4 pmol/l (13.1 ng/dl) in Case 7, of 189.3 pmol/l (5.1 ng/dl)

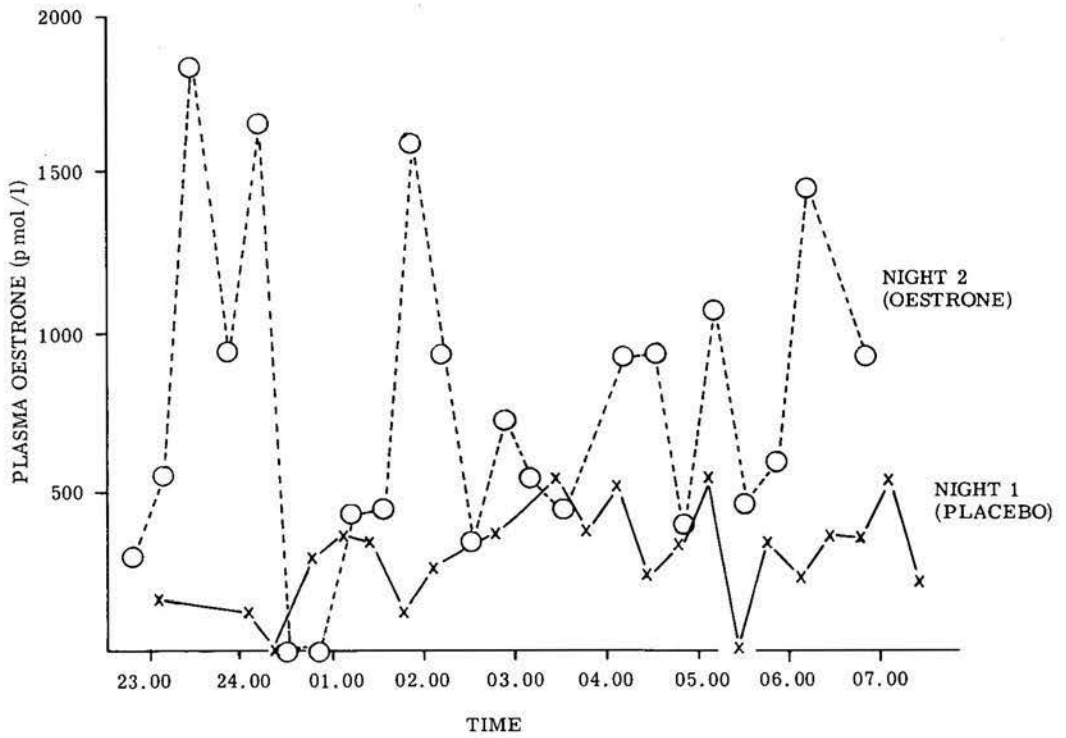


FIG. 22: Nocturnal plasma oestrone levels (pmol/l) in Case 10 on placebo (Night 1) and after one month of treatment with piperazine oestrone sulphate 3 mg/day (Night 2).

in Case 8, and of 428.0 pmol/l (11.6 ng/dl) in Case 10. When the oestrone levels on the two nights were compared using a t-test for paired observations, the change was short of significant in Case 9 ($t = 1.212$), but the oestrone concentrations were significantly higher on the second blood night in Case 7 ($t = 2.875$, $p < 0.02$), Case 8 ($t = 4.886$, $p < 0.001$), and Case 10 ($t = 3.801$, $p < 0.001$).

TABLE 19: Mean Nocturnal Plasma Oestrone Concentration \pm Standard Error of the Mean (pmol/l).

Case Number	Night 1	Night 2
<u>Placebo Group</u>		
1	293.2 \pm 151.0	586.8 \pm 60.1
2	155.1 \pm 36.5	148.4 \pm 31.6
3	155.5 \pm 68.5	66.9 \pm 16.5
4	209.2 \pm 16.8	175.7 \pm 18.7
5	494.9 \pm 24.3	324.8 \pm 56.8
6	147.6 \pm 32.0	128.2 \pm 15.2
Mean	242.6	238.4
<u>Oestrone Group</u>		
7	252.4 \pm 54.7	735.8 \pm 150.2
8	108.7 \pm 23.6	298.0 \pm 30.7
9	278.4 \pm 37.1	359.9 \pm 58.2
10	290.0 \pm 33.3	718.0 \pm 110.0
11	161.3 \pm 39.6	-
12	221.7 \pm 42.9	-
Mean	218.8	527.9

The mean levels of the two groups were similar on the first blood night, that of the oestrone group being 218.8 pmol/l (5.9 ng/dl) and that of the placebo group 242.6 pmol/l

(6.6 ng/dl). Although there was considerable variation in individual cases, the mean level of the placebo group showed little change between the two blood nights, with a mean decrease of only 4.2 pmol/l (0.1 ng/dl). The oestrone group showed a mean increase of 295.5 pmol/l (8.0 ng/dl), and when the changes in the two groups were compared using the Mann-Whitney U test the difference between them was significant ($U = 3$, $p < 0.033$).

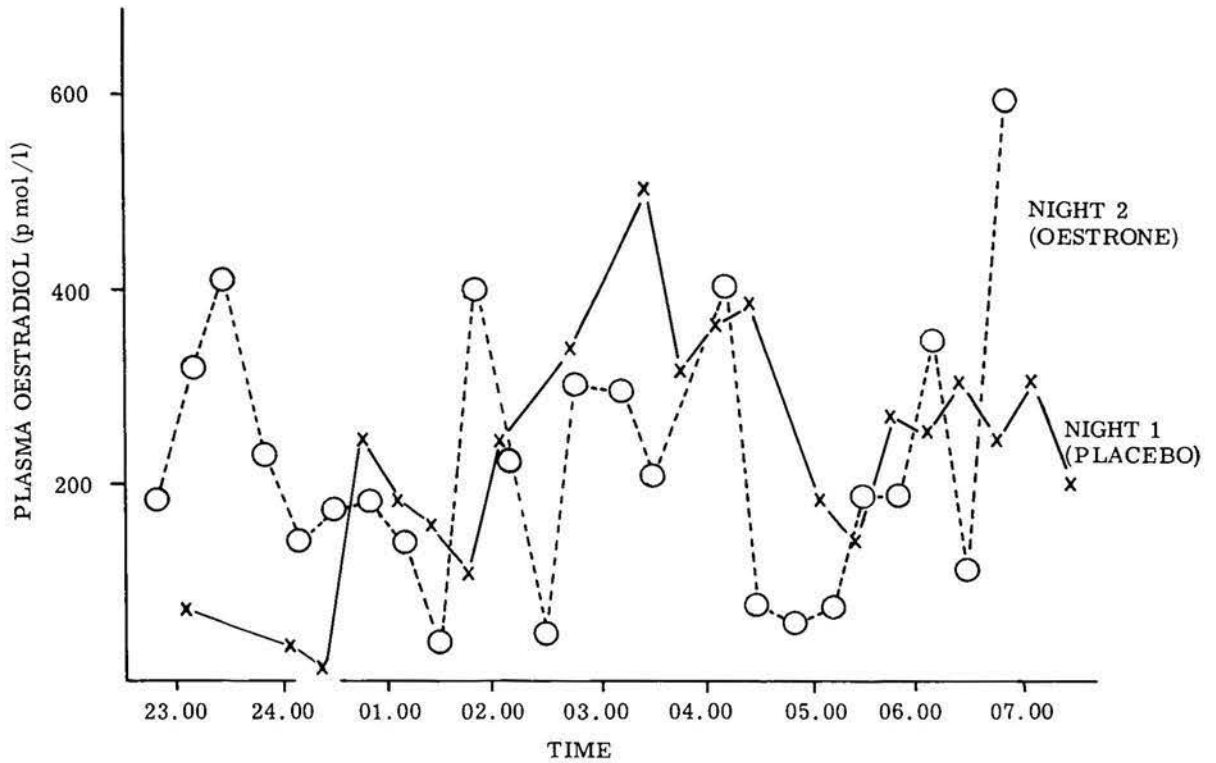
There was no significant correlation between the mean oestrone level and the duration of amenorrhoea ($r_s = 0.45$, N.S.), though the mean oestrone levels were higher in patients with amenorrhoea for less than one year.

There was no evidence of a diurnal rhythm in oestrone levels during the night. Fluctuations in the oestrone level were irregular, and when the night is divided into three periods, there was no significant difference between the mean levels of each period.

The changes in hormone level bore no relationship to changes in sleep stages, and there was no correlation between mean oestrone levels and sleep latency, sleep duration, or the amount of any sleep stage.

Oestradiol

The oestradiol levels also fluctuated rapidly during the night both when on placebo and when on oestrogen treatment, as can be seen from Fig. 23, showing the oestradiol levels of Case 10 on the two blood nights. The mean levels for the two nights are shown in Table 20, and from this it



can be seen that some of the patients had oestradiol levels similar to those of the early menstrual cycle, while others had very low levels. There was a significant correlation between the mean oestradiol level and duration of amenorrhoea ($r_s = 0.55$, $p < 0.05$), but it can be seen from Fig. 24 that the level was highest in patients with amenorrhoea for less than one year, and there was little difference in the hormone levels in relation to the duration of amenorrhoea after this.

TABLE 20: Mean Nocturnal Plasma Oestradiol Concentration \pm Standard Error of the Mean (pmol/l).

Case Number	Night 1	Night 2
<u>Placebo Group</u>		
1	171.7 \pm 43.7	251.8 \pm 49.9
2	46.4 \pm 14.1	37.5 \pm 10.9
3	46.8 \pm 17.4	42.3 \pm 10.2
4	54.3 \pm 5.2	110.8 \pm 19.2
5	158.6 \pm 20.6	61.4 \pm 15.7
6	78.8 \pm 22.8	100.3 \pm 58.7
Mean	92.8	100.7
<u>Oestrone Group</u>		
7	26.9 \pm 12.8	181.5 \pm 23.2
8	47.7 \pm 17.0	149.3 \pm 41.1
9	174.0 \pm 27.2	74.7 \pm 13.5
10	231.5 \pm 27.7	226.3 \pm 29.0
11	63.4 \pm 16.6	\pm
12	93.5 \pm 36.2	-
Mean	106.2	158.0

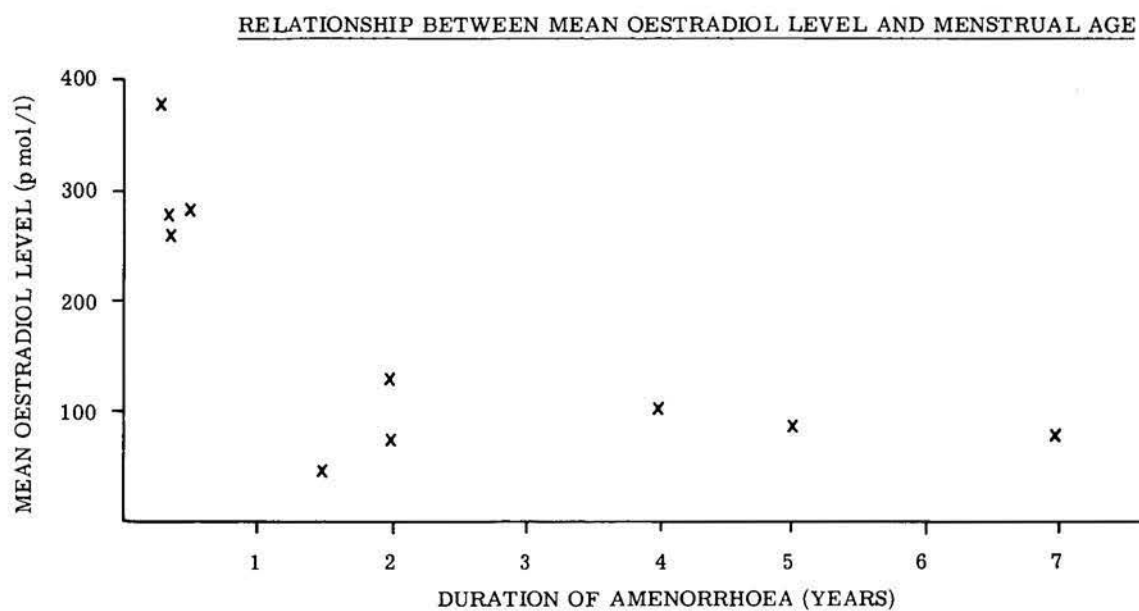


FIG. 24: The relationship between the duration of amenorrhoea and the mean plasma oestradiol concentration on the first night of the study.

Comparing the magnitude of change in the two groups between the first and second blood nights, the oestrone group had a mean increase of 37.9 pmol/l (1.0 ng/dl) and the placebo group a mean increase of 7.9 pmol/l (0.2 ng/dl) but because of the wide variation in individual results the difference between the groups was not significant ($t = 0.548$).

Some of the patients in the placebo group showed a marked change in their mean oestradiol levels between the two nights. Case 1 showed a mean increase of 80.1 pmol/l (2.2 ng/dl), and Case 4 an increase of 56.5 pmol/l (1.5 ng/dl), while Case 5 showed a decrease of 97.2 pmol/l (2.6 ng/dl). When the oestradiol levels on the two nights were compared using a t-test for paired observations, the difference was significant in Case 4 ($t = 3.118$, $p < 0.005$) and Case 5 ($t = 3.716$, $p < 0.001$), but the change shown by Case 1 was short of significance ($t = 0.680$).

The patients in the oestrone group did not show a consistent pattern of change in their plasma oestradiol concentrations between the first and second nights of the study. The mean oestradiol level of Case 7 increased by 154.6 pmol/l (4.2 ng/dl), and Case 8 had a smaller increase of 101.6 pmol/l (2.8 ng/dl), but Case 9 showed a decrease of 99.3 pmol/l (2.7 ng/dl) and Case 10 a decrease of 5.2 pmol/l (0.1 ng/dl). When the plasma oestradiol concentrations of the two nights were compared, they were found to be significantly higher on the second night in Case 7 ($t = 5.279$, $p < 0.001$) and in Case 8 ($t = 2.656$,

$p < 0.02$), and significantly lower in Case 9 ($t = 3.125$, $p < 0.005$), but the difference was not significant in Case 10 ($t = 0.135$). When the magnitude of change in the two groups was compared, the difference between the groups was not significant.

There was no evidence of a diurnal rhythm in oestradiol levels, and the changes were irregular and bore no relationship to changes in sleep stages. There was no correlation between mean oestradiol level and either sleep latency, duration, or the amount of any sleep stage, nor was there any difference in the mean oestradiol levels in each sleep stage.

There was a significant positive correlation between the mean oestrone and mean oestradiol levels in the twelve patients on night 1 ($r = 0.59$, $p = 0.05$) and the six patients on placebo on night 2 ($r = 0.84$, $p = 0.05$), but in the oestrone group in the second blood night the correlation was short of significance, possibly because of the small number of patients. However, when the changes in the two hormones throughout the night in each patient are considered, there was no consistent relationship between the oestrone and oestradiol levels.

Oestrone : Oestradiol Ratio

It can be seen from Table 21 that the oestrone : oestradiol ratio varied widely, but in all cases was greater than 1. The lowest value was that of Case 10, who had a ratio of 1.3:1, and the highest was that of Case 7, who had

a ratio of 9.3:1 after 18 months amenorrhoea. In both groups there was considerable variation between the two blood nights, and oestrogen treatment had no consistent effect on the ratio, increasing it in two cases and decreasing it in two.

There was no significant correlation between the oestrone: oestradiol ratio and the duration of amenorrhoea.

TABLE 21: Mean Oestrone : Oestradiol Ratio

Case Number	Night 1	Night 2
<u>Placebo Group</u>		
1	1.7:1	2.2:1
2	3.3:1	3.9:1
3	3.3:1	1.6:1
4	3.8:1	1.6:1
5	3.1:1	5.3:1
6	1.9:1	1.3:1
<u>Oestrone Group</u>		
7	9.3:1	4.0:1
8	2.3:1	2.0:1
9	1.6:1	4.8:1
10	1.3:1	3.2:1
11	2.5:1	-
12	2.4:1	-

Prolactin

The mean nocturnal plasma prolactin concentration varied widely between patients and also between nights, as can be seen from Table 22. On the first night, when all patients were on placebo, it varied from 124.1 mIU/l (6.2 ng/ml) to 990.8 mIU/l (49.5 ng/ml), with the mean

value of the placebo group, 269.2 mIU/l (13.5 ng/ml) being much lower than that of the oestrone group, 410.6 mIU/l (20.5 ng/ml), though the difference between the two groups was not significant ($t = 1.42$, N.S.). Although the group mean nocturnal plasma prolactin level of the placebo group on the second night was similar to that of the first night, the individual patients showed considerable variation, with Case 2 showing a decrease of 163.8 mIU/l and Case 4 an increase of 176.6 mIU/l. Oestrogen treatment had no consistent effect on the mean nocturnal plasma prolactin levels of the oestrone group, and only one patient, Case 7, showed a large increase of 294.4 mIU/l, while one showed a smaller increase, one a decrease and another no change. There was no significant difference in the magnitude of change between the two nights in the oestrone and placebo group.

TABLE 22: Mean Nocturnal Plasma Prolactin Concentration \pm Standard Error of the Mean (mIU/l).

Case Number	Night 1	Night 2
<u>Placebo Group</u>		
1	206.6 \pm 26.1	222.0 \pm 12.0
2	436.6 \pm 26.1	272.8 \pm 36.1
3	240.8 \pm 36.1	291.0 \pm 64.1
4	221.0 \pm 20.0	397.6 \pm 32.1
5	208.4 \pm 34.1	144.0 \pm 14.0
6	301.4 \pm 66.1	435.0 \pm 110.2
Mean	269.2	293.8
<u>Oestrone Group</u>		
7	990.8 \pm 102.2	1285.2 \pm 98.2
8	574.4 \pm 70.1	435.0 \pm 72.1
9	274.4 \pm 20.0	273.4 \pm 30.1
10	370.4 \pm 58.1	553.6 \pm 46.1
11	124.4 \pm 28.1	-
12	129.2 \pm 32.1	-
Mean	410.6	636.8

Nocturnal prolactin secretion is known to show a sleep dependent increase, so the results have been analysed in relation to sleep onset. The levels of all patients were lower before sleep onset than during sleep on both nights, but varied from 0 to 300.0 mIU/l (0-15 ng/ml). In the placebo group, the mean plasma prolactin concentration before sleep onset of 138.0 ± 52.0 mIU/l (6.9 ± 2.6 ng/ml) on the first night was higher than that on the second blood night, 46.0 ± 46.0 mIU/l (2.3 ± 2.3 ng/ml). In the oestrone group, one patient, Case 7, fell asleep before the first blood sample could be taken on both nights, but the mean plasma prolactin level before sleep onset of the remaining patients was 84.0 ± 60.0 mIU/l (4.2 ± 3.0 ng/ml) on the first night and 134.0 ± 134.0 mIU/l (6.7 ± 6.7 ng/ml) on the second night.

The plasma prolactin concentration increased within 60-90 minutes of sleep onset in all cases except Case 9 on the first night, when it took 160 minutes, and Case 5 on the second night, when it took 140 minutes. This increase in secretion lasted for 6-8 hours, but the pattern of the increase, and the peak levels, showed considerable individual variation. Case 7 had a rapid rise with a series of very high peaks on both nights, as can be seen from Fig. 25, and had much higher levels than the other patients. Other patients, e.g. Cases 3 and 10, had a single high peak, and others a series of lower peaks. The peak prolactin values ranged from 284.0 to 1620.0 mIU/l ($14.2 - 81.0$ ng/ml) on the first night, as can be seen

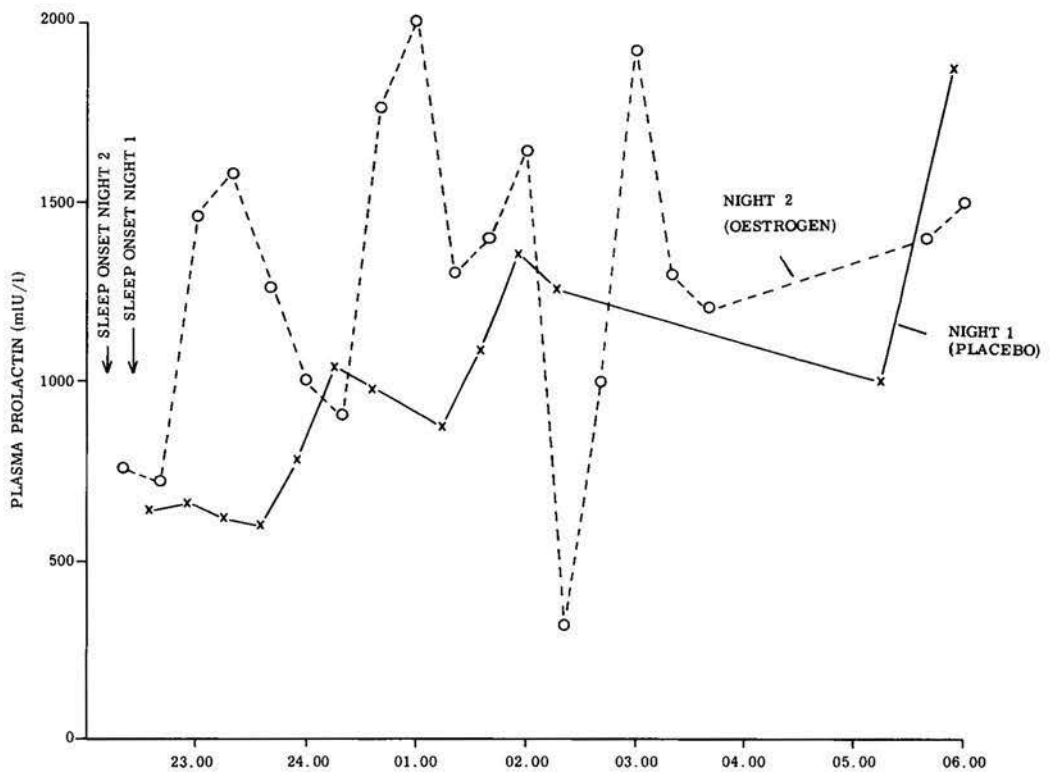


FIG. 25: Nocturnal plasma prolactin concentrations (mIU/l) in Case 7 on placebo (Night 1) and after one month of treatment with piperazine oestrone sulphate 3 mg/day (Night 2).

from Table 23, and the mean peak prolactin of the oestrone group was significantly higher than that of the placebo group on this night ($t = 3.130$, $p < 0.02$). In both groups, some patients had higher peak values and some lower on the second blood night and oestrogen treatment had no consistent effect on the magnitude of the peak values, with two patients showing an increase and two a decrease in their peak prolactin levels.

TABLE 23: Peak Nocturnal Plasma Prolactin Concentration(mIU/l)

Case Number	Night 1	Night 2
<u>Placebo Group</u>		
1	284.0	312.0
2	660.0	510.0
3	580.0	970.0
4	392.0	580.0
5	294.0	480.0
6	790.0	620.0
Mean	500.0	578.6
<u>Oestrone Group</u>		
7	1620.0	1960.0
8	1110.0	730.0
9	430.0	470.0
10	984.0	940.0
11	554.0	-
12	406.0	-
Mean	850.6	1025.0

The results of the two groups have also been analysed as hourly mean levels after sleep onset on each night, as shown in Figs. 26 and 27. In the placebo group there was

a clear increase in plasma prolactin concentrations after sleep onset and there was little difference in the pattern of secretion or levels of prolactin on the two nights. From comparing the two figures, it can be seen that the oestrone group had higher mean levels than the placebo group on both nights. The nocturnal increase in prolactin secretion occurred more rapidly when the patients were on oestrogen treatment but there was little difference in the peak levels on the two nights. However, if the results of individual patients are considered, instead of the group mean, it can be seen that the response varied considerably between patients. The two patients who showed the greatest increase in their plasma oestrogen concentrations showed the most marked change in their prolactin secretions. Case 7 showed an earlier increase in her prolactin secretion when on oestrogen treatment, with a series of higher peaks (see Fig. 25), and Case 10 showed an earlier and more prolonged increase, with a series of lower peaks instead of a single high peak (see Fig. 28). Cases 8 and 9, who had smaller increases in their plasma oestrone levels, showed no clear change in either the pattern of secretion or the concentrations of prolactin on oestrogen treatment.

There was no relationship between changes in prolactin and changes in concentration in oestrone or oestradiol during the night, nor was the correlation between mean or peak prolactin levels and mean oestrogen levels significant. The correlation coefficient between peak nocturnal prolactin levels and mean oestrone concentration was 0.90 on the

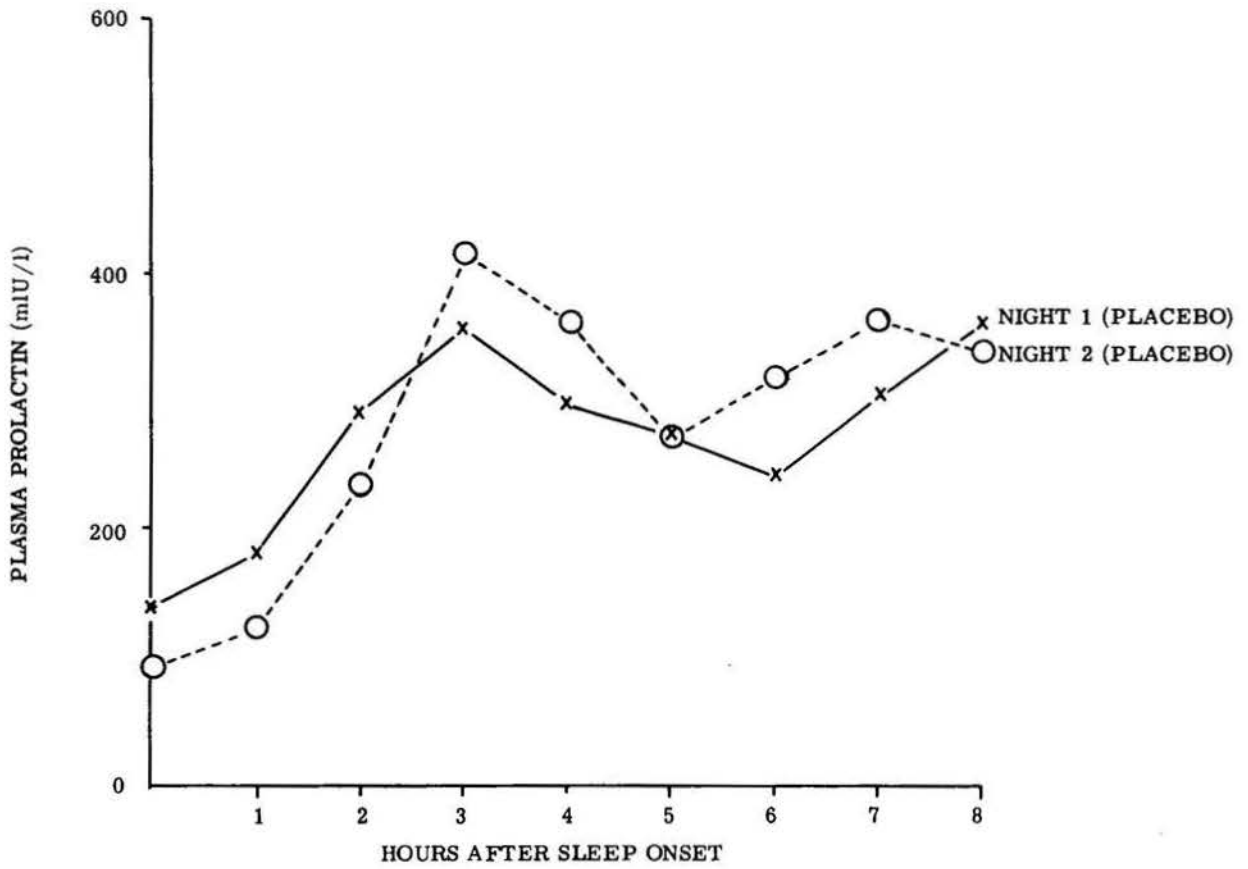


FIG. 26: Hourly mean prolactin levels (mIU/l) in relation to sleep onset in the placebo group.

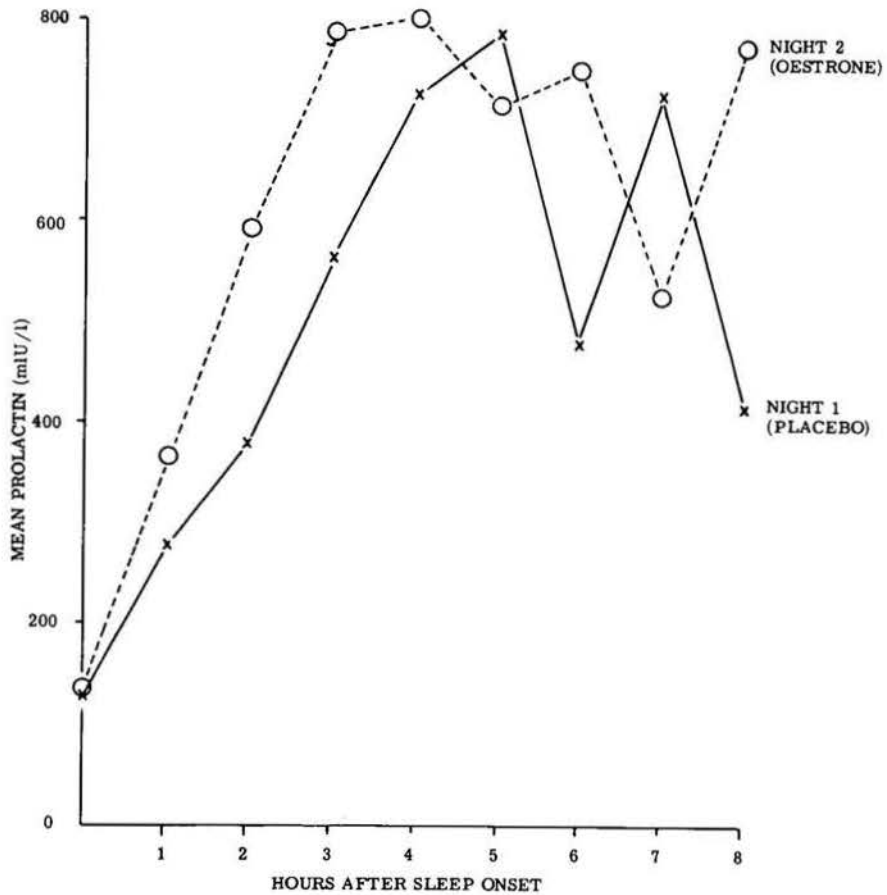


FIG. 27: Hourly mean prolactin concentrations (mIU/l) in relation to sleep onset in the oestrone group.

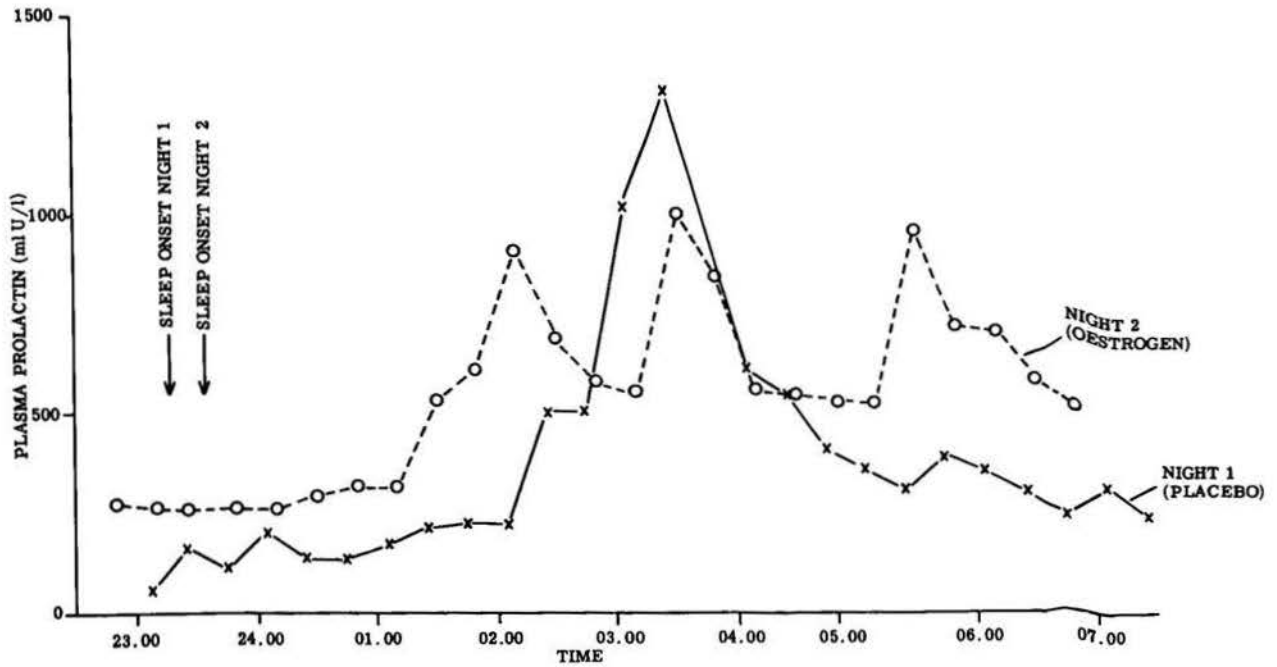


FIG. 28: Nocturnal plasma prolactin concentrations (mIU/l) in Case 10 on placebo (Night 1) and after one month of treatment with piperazine oestrone sulphate 3 mg/day (Night 2)

second night in the oestrone group, and between mean prolactin concentration and mean oestrone concentration was 0.88, but because of the small numbers this was not statistically significant. The correlations between mean and peak prolactin concentrations and total plasma oestrogen concentration were lower ($r = 0.85$, $r = 0.83$) and again these correlations were not significant. There was no evidence of a relationship between either mean or peak prolactin concentrations and age or duration of amenorrhoea.

On the first blood night, there was a significant positive correlation between the mean plasma prolactin concentration and the amount of slow wave sleep when all twelve patients were considered ($r = 0.66$, $p < 0.05$), but this was not found on the second night in either group. Other than this, there was no correlation between either mean or peak plasma prolactin concentration and the amount of any sleep stage, sleep onset latency, or sleep duration. The changes in prolactin levels during the night bore no relationship to changes in sleep stage, and the mean concentration of prolactin was no different during REM sleep or slow wave sleep from that in the other sleep stages.

Tryptophan

Because of a laboratory accident, only samples from the first blood night in Cases 4 and 5 and the second blood night in Case 1 were analysed. The patients were receiving placebo on these nights, so no information is available on the effect of oestrogen treatment on plasma tryptophan levels.

The mean total plasma tryptophan concentrations were $72.6 \pm 2.2 \mu\text{mol/l}$ ($14.8 \pm 0.5 \mu\text{g/ml}$) in Case 1, $67.1 \pm 1.1 \mu\text{mol/l}$ ($13.7 \pm 0.2 \mu\text{g/ml}$) in Case 4, and $65.7 \pm 1.9 \mu\text{mol/l}$ ($13.4 \pm 0.4 \mu\text{g/ml}$) in Case 5. The mean free plasma tryptophan concentrations were $9.0 \pm 0.7 \mu\text{mol/l}$ ($1.8 \pm 0.1 \mu\text{g/ml}$) in Case 1, $4.4 \pm 0.2 \mu\text{mol/l}$ ($0.9 \pm 0.0 \mu\text{g/ml}$) in Case 4, and $7.0 \pm 0.4 \mu\text{mol/l}$ ($1.4 \pm 0.1 \mu\text{g/ml}$) in Case 5. The results were also considered as % free plasma tryptophan, and the mean values for the three patients were $12.2 \pm 0.9\%$, $6.6 \pm 0.2\%$, and $10.6 \pm 0.5\%$ respectively.

Both free and total plasma tryptophan levels fluctuated during the night in all three cases (see Figs. 29 and 30). In Cases 1 and 4 there was a significant positive correlation between free and total plasma tryptophan concentrations (Case 1, $r = 0.65$, Case 4 $r = 0.54$, $p < 0.01$ in both cases), but in Case 5 the correlation was not significant ($r = 0.31$, N.S.). The total plasma tryptophan levels were lowest in the early hours of the morning, as can be seen from inspection of Fig. 30, and to seek evidence of a diurnal variation, the results were analysed by dividing the night into three periods (P1, P2, and P3) using 2 a.m. and 5 a.m. as cut off points, as described by Chen et al (1974). Table 24 shows the mean total plasma tryptophan concentrations in the three periods, and it can be seen that in all three patients the levels were lowest in P2. The difference between the three periods was significant, $\chi^2_r = 9.33$, $p < 0.028$.

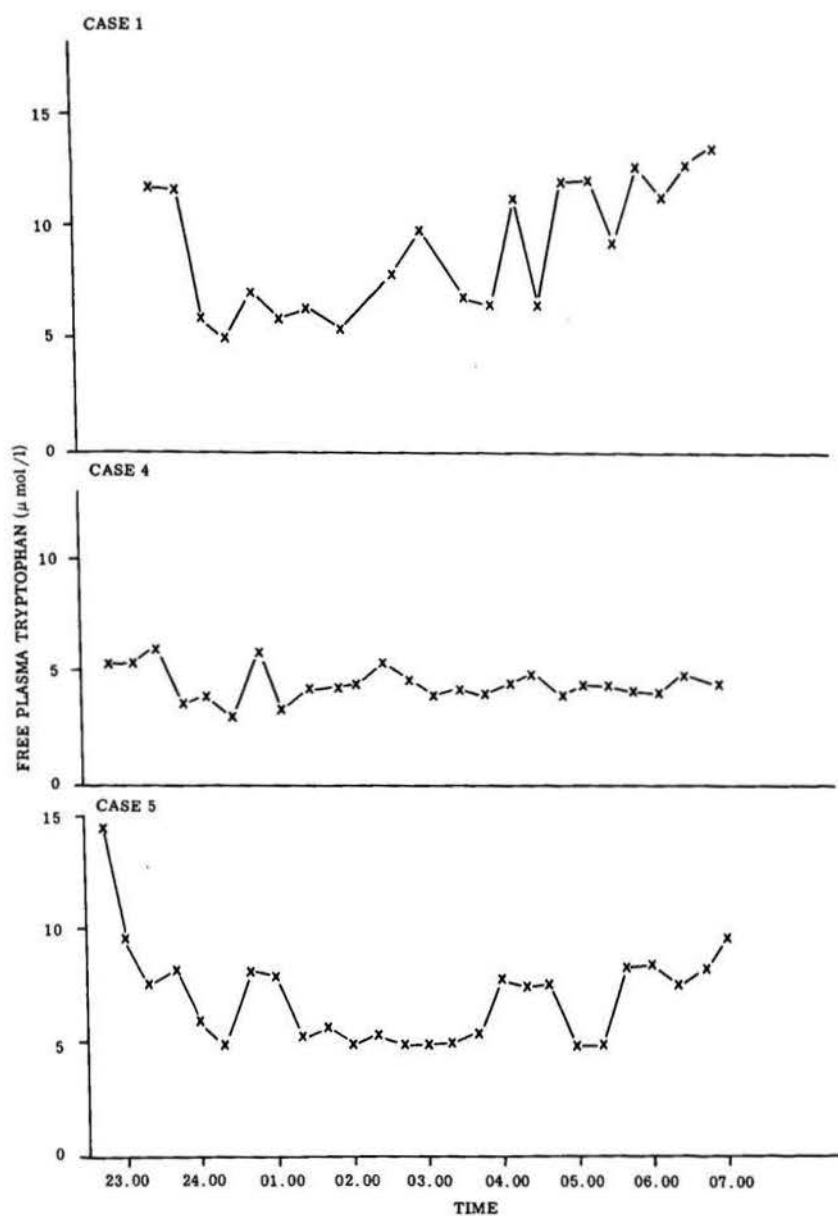


FIG. 29: Nocturnal free plasma tryptophan concentrations ($\mu\text{mol/l}$) in Case 1 on Night 2 (on placebo) and in Cases 4 and 5 on Night 1 (on placebo).

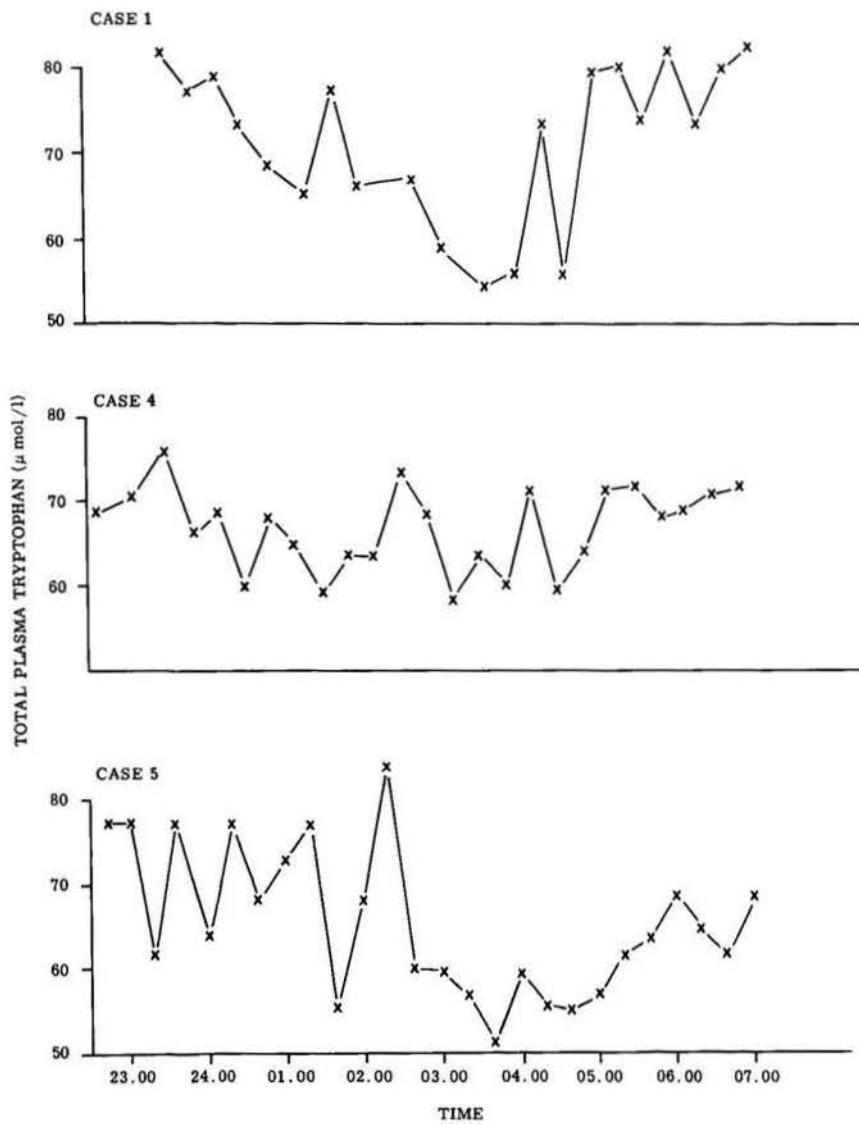


FIG. 30: Nocturnal total plasma tryptophan concentrations ($\mu\text{mol/l}$) in Case 1 on Night 2 (on placebo) and in Cases 4 and 5 on Night 1 (on placebo).

TABLE 24: Total Plasma Tryptophan Concentrations \pm Standard Error of the Mean ($\mu\text{mol/l}$) in Three Periods of the Night.

Case Number	Sleep Periods		
	P1 (Up to 1.59a.m.)	P2 (2a.m. to 4.59a.m.)	P3 (After 5 a.m.)
1	75.7 \pm 2.5	61.7 \pm 3.0	80.2 \pm 1.6
4	66.8 \pm 1.7	64.8 \pm 1.9	71.0 \pm 0.7
5	71.4 \pm 2.8	60.9 \pm 3.5	63.7 \pm 1.7

Although there was no obvious pattern of change in the levels of free plasma tryptophan during the night, these results too were analysed by comparing the mean values of three periods of the night, as described for total plasma tryptophan. These results are shown in Table 25, and it can be seen from this that although the free plasma tryptophan levels were lowest in P2 in Cases 1 and 5, they were highest at this time in Case 4, and there was no consistent pattern in the three patients, and the difference between the three periods of the night was not significant ($\chi^2_r = 2.08$).

TABLE 25: Mean Free Plasma Tryptophan Concentrations \pm Standard Error of the Mean ($\mu\text{mol/l}$) in Three Periods of the Night.

Case Number	Sleep Periods		
	P1 (Up to 1.59a.m.)	P2 (2a.m. to 4.59a.m.)	P3 (After 5 a.m.)
1	7.7 \pm 1.1	7.4 \pm 0.9	11.9 \pm 0.6
4	4.4 \pm 0.3	4.5 \pm 0.2	4.4 \pm 0.1
5	7.8 \pm 0.9	5.9 \pm 0.4	7.4 \pm 0.7

There was a high correlation between changes in free plasma tryptophan and plasma oestrogens, as can be seen from Table 26. The correlation between the free plasma tryptophan and total plasma oestrogen concentration (oestrone + oestradiol) was highly significant in all three cases (Case 1, $r = 0.91$, $p < 0.001$; Case 4, $r = 0.87$, $p < 0.001$; Case 5, $r = 0.49$, $p < 0.01$). When the relationship with plasma oestrone alone is considered, the correlation is lower but still significant in all three cases (Case 1, $r = 0.64$, $p < 0.01$; Case 4, $r = 0.83$, $p < 0.001$; Case 5, $r = 0.46$, $p < 0.05$), but the correlation between free plasma tryptophan concentration and plasma oestradiol concentration is significant only in Case 1 ($r = 0.62$, $p < 0.01$). The relationship between total plasma oestrogen concentration and % free plasma tryptophan is even closer, and it can be seen from inspection of Figs. 31, 32 and 33 that they change almost in parallel during the night in each case. The correlation coefficient r between the total plasma oestrogen concentration and % free plasma tryptophan was 0.99 in Case 1, 1.00 in Case 4, and 0.81 in Case 5 ($p < 0.001$ in all cases). The correlation between plasma oestrone concentrations and % free plasma tryptophan is also significant, though lower than the correlation between % free tryptophan and total oestrogen levels, and the correlation with plasma oestradiol is again lower, but significant in Cases 1 and 5, but not Case 4 (see Table 26). There was no significant correlation between total plasma tryptophan concentration and the concentration of either oestrone, oestradiol, or total plasma oestrogens.

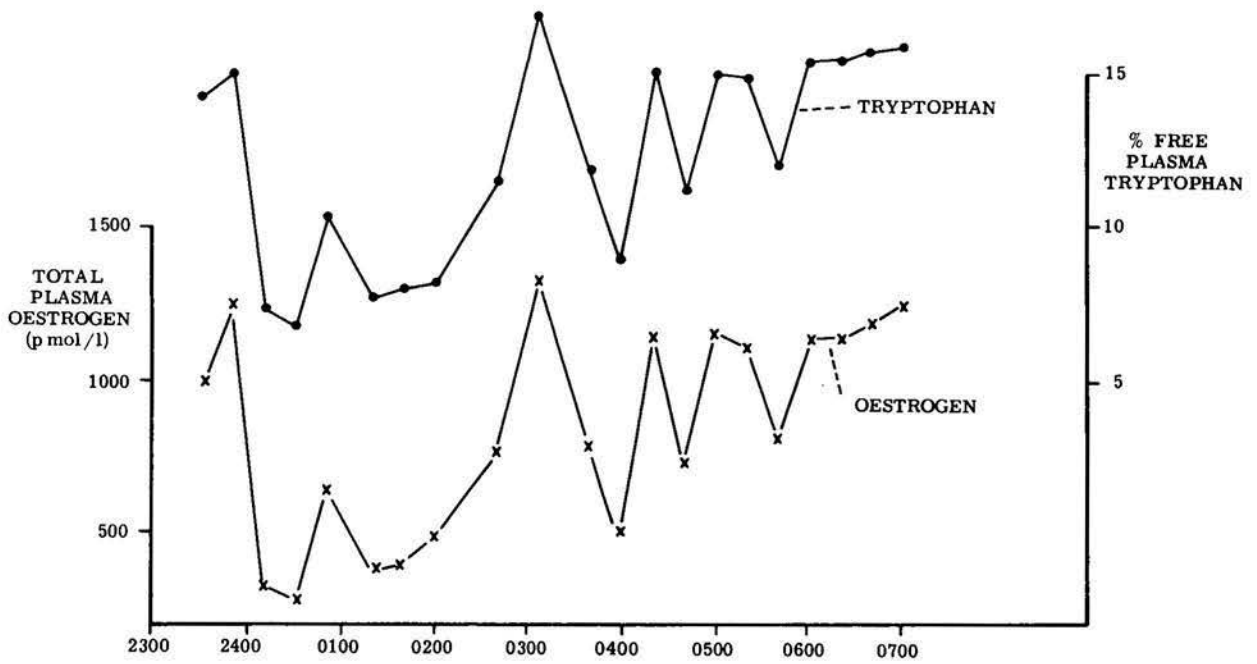


FIG. 31: Total plasma oestrogen concentrations (pmol/l) and % free plasma tryptophan in Case 1 during Night 2 (on placebo).

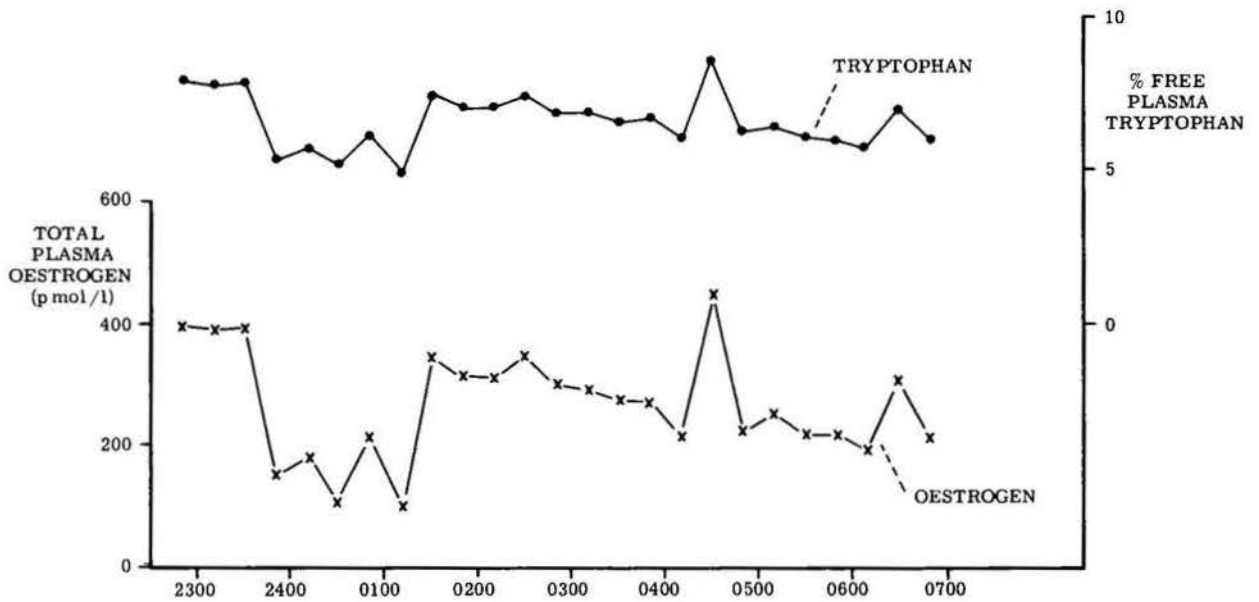


FIG. 32: Total plasma oestrogen concentrations (pmol/l) and % free plasma tryptophan in Case 4 during Night 1 (on placebo).

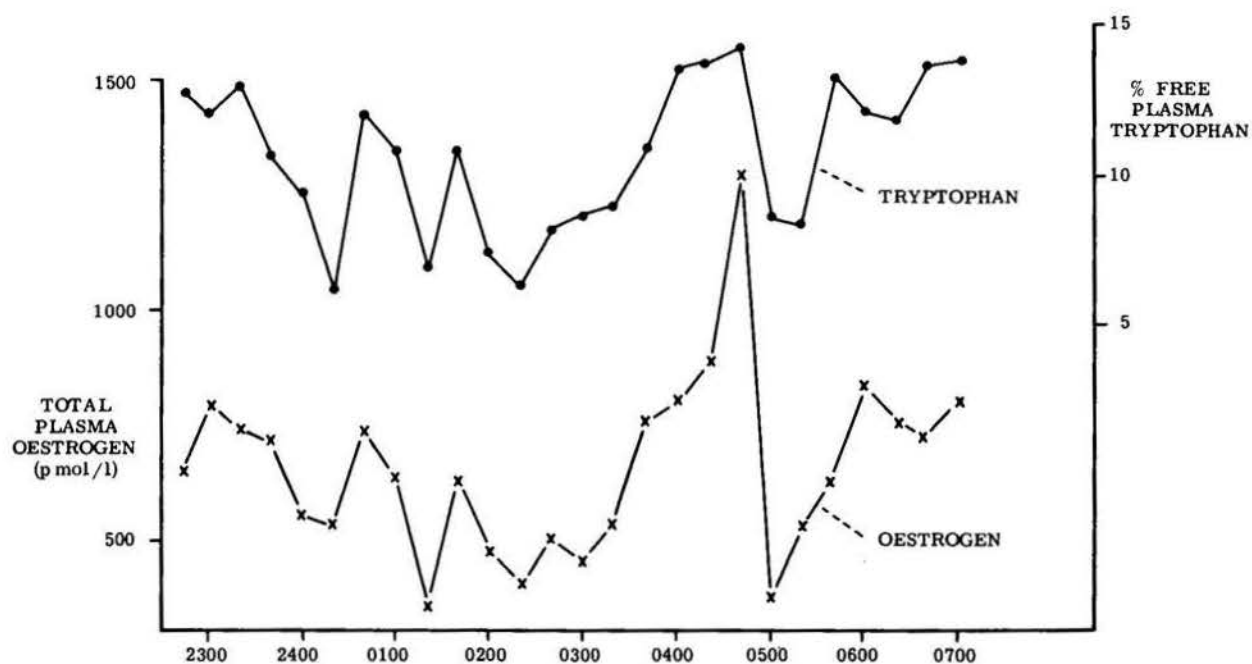


FIG. 33: Total plasma oestrogen concentrations (pmol/l) and % free plasma tryptophan in Case 5 during Night 1 (on placebo).

TABLE 26: The Relationship Between Free Plasma Tryptophan Concentration and Plasma Oestrogen and Prolactin Concentrations.

	Correlation Coefficient r					
	Case 1		Case 4		Case 5	
	r	p	r	p	r	p
Plasma oestrone	0.64	<0.01	0.83	<0.001	0.46	<0.05
Plasma oestradiol	0.62	<0.01	0.34	N.S.	0.37	N.S.
Total plasma oestrogens	0.91	<0.001	0.87	<0.001	0.49	<0.01
Plasma prolactin	-0.41	<0.05	-0.07	N.S.	-0.50	<0.01

TABLE 27: The Relationship Between % Free Plasma Tryptophan and Plasma Oestrogen and Prolactin Concentrations.

	Correlation Coefficient r					
	Case 1		Case 4		Case 5	
	r	p	r	p	r	p
Plasma oestrone	0.78	<0.001	0.96	<0.001	0.71	<0.001
Plasma oestradiol	0.57	<0.01	0.35	N.S.	0.68	<0.001
Total Plasma oestrogen	0.99	<0.001	1.00	<0.001	0.81	<0.001
Prolactin	-0.51	<0.01	0.08	N.S.	-0.40	<0.05

In Cases 1 and 5 there was a significant inverse correlation between plasma prolactin concentration and both concentration and % free plasma tryptophan, but in Case 4 the relationship was not significant, and none of the patients showed a correlation between plasma prolactin and total plasma tryptophan concentrations.

There was no direct temporal relationship between changes in either free or total plasma tryptophan concentration and any sleep stage and the number of patients studied is insufficient to demonstrate any significant relationship between sleep duration, sleep latency, or the amount of any sleep stage and the mean concentrations of either total or free plasma tryptophan.

DISCUSSION

SLEEP

In my study, visual analogue scales of sleep quality have failed to show that oestrogen is significantly more effective than placebo in improving the sleep quality of menopausal women. This agrees with the results of Utian (1972a). He found that oestrogen was no more effective than placebo in relieving insomnia in oophorectomized women, but he used a global scale of severity of insomnia rated 0-3, and this may not have been sufficiently sensitive to show a change. Campbell (1976b) carried out two double-blind cross-over studies, one lasting for four months in patients with severe menopausal symptoms, and one lasting a year in patients with mild symptoms. Using a visual analogue scale of insomnia, he found that oestrogen was significantly more effective than placebo in relieving insomnia in patients with severe symptoms, but not in those with mild symptoms. My patients may resemble the patients with "mild" symptoms in his study rather than those with "severe" symptoms, but as he gives no further details of their symptoms it is not possible to be certain of this. There were differences between my study design and that of Campbell (1976b) in that his was a cross-over study and mine a comparison between groups, and also differences in the administration of our rating scales, as my patients completed their scales every day, and his completed them only once in two months. We used different visual

analogue scales, since his measured insomnia and mine sleep quality, and, in rating their sleep quality, patients take into account not only their sleep duration and frequency of wakings, but also whether they had bad dreams, felt they had slept deeply, or felt unrefreshed in the morning.

Visual analogue scales of sleep quality gave different results from the electrophysiological recording of sleep in my study. This may in part be due to their measuring different things, since the visual analogue scales of sleep measure how satisfied the patients are with their sleep, and the sleep record shows precisely how long the patient spent awake and asleep during the night. Visual analogue scales are less sensitive than the objective, electrophysiological measures of sleep, and it is possible that a larger number of patients would be needed to demonstrate a difference between the two groups by the visual analogue method.

Electrophysiological recording of sleep showed a wide variation between patients in sleep latency, sleep duration, and the number and duration of episodes of intervening wakefulness. There was no consistent pattern of sleep disturbance, and although all of the patients complained of insomnia, some appeared to sleep well and had a sleep duration of eight hours, while others had only a few minutes of intervening wakefulness. This finding is not surprising, since numerous studies have failed to

demonstrate any consistent abnormality in the sleep patterns of insomnia patients. There are wide individual differences in sleep duration and pattern, and in a recent review of research on insomnia Beutler et al (1978) remarked that not all who complain of insomnia have an abnormal sleep pattern, nor do all people with an abnormal sleep pattern complain of insomnia.

Oestrogen treatment decreased the number and duration of episodes of wakefulness that interrupt sleep in perimenopausal women in my study. There was little change in intervening wakefulness in the placebo group throughout the study, but in the oestrone group it was decreased in the first month of active treatment, and in the second treatment month there was a further decrease in the amount of intervening wakefulness and also a decrease in the number of episodes of wakefulness. Analysis of the distribution of wakefulness during the night showed that oestrogen treatment decreased the amount of intervening wakefulness throughout the night, not just at the beginning or end of the sleep period. In the oestrone group, there was no increase in the amount of stage 1 sleep in either treatment month, so the decrease in intervening wakefulness cannot have been due to an increase in the amount of drowsiness. There was an increase in the total number of shifts to stage 1 sleep in the oestrone group in the first treatment month, which was significant when compared to the small decrease shown by the placebo group. Since the amount of stage 1 sleep was unchanged

this means that the patients had more arousals but went back to sleep more quickly. When the number of shifts to stage 1 in each hour of sleep are examined, it can be seen that there are more arousals in the third hour of sleep in the first treatment month than in the baseline period in the oestrone group, but that this accounts for only part of the increase. The oestrone group had a longer sleep duration in the first treatment month than in the baseline period, and when the sleep duration is kept constant, i.e. when the results are considered in terms of the first six hours of sleep, the difference between the groups is no longer significant, so much of this increase in the number of shifts to stage 1 must be due to the patients sleeping longer.

Between the baseline period and the first treatment month the oestrone group showed an increase in the number of shifts to stage 2 sleep, which simply means that after arousal to stage 1 the patients sank back into a deeper sleep. This increase too was short of significance when the results were considered in terms of the first six hours of sleep, indicating that the change was related to a longer sleep duration. In the second treatment month, the number of shifts to sleep stages 1 and 2 returned to baseline levels in both groups.

Sleep onset latency decreased slightly in both groups throughout the study, and the patients also slept longer as the study progressed, and this may have been due to the improvement in their symptoms or to their growing more

used to the sleep laboratory. There was no evidence that oestrogen treatment had any effect on sleep onset latency, and although the increase in sleep duration was greater in the oestrone than in the placebo group, the difference between the two was not significant. In both groups, the increase in sleep duration led to an increase in the amount of stage 2 sleep, as this is the commonest sleep stage and occupies most of the night between periods of REM sleep. REM sleep periods become longer and more frequent towards the end of the night, so it is not surprising that the amount of REM sleep also increased with the increase in sleep duration, or that the increase in REM sleep was greatest in the oestrone group. Slow wave sleep was not changed in either group, and there were no changes in the amount of any sleep stage in the first six hours of sleep, or in the distribution of the sleep stages during the night, other than the changes in intervening wakefulness.

In a double blind study patients are randomly allocated to treatment groups, and it is always possible that the groups will not be comparable by chance. In my study the two groups had similar results during the baseline period for all parameters except for intervening wakefulness. The oestrone group had more broken sleep than the placebo group, and although the difference between them was not significant, the conclusion that oestrogen improves sleep could have been more confidently derived had the groups been more closely matched. It

is possible that the patients with a very high level of intervening wakefulness adapt only slowly to the sleep laboratory, and that the effect of oestrone treatment is an artefact due to there being more patients with very disturbed sleep in this group. However, inspection of the results of individual patients shows that the improvement in intervening wakefulness in the oestrone group is not confined to patients with a high level of intervening wakefulness, and only one patient in the placebo group with very disturbed sleep showed an improvement. Twelve patients in the oestrone group showed a decrease in intervening wakefulness, compared with only five in the placebo group, and the magnitude of the change was much greater in the oestrone group, so the difference between the groups is not likely to be due to an artefact. In absolute terms the decrease in intervening wakefulness is relatively small, and was insufficient to cause a difference between the two groups on the visual analogue scales of sleep quality, so it is unlikely that this effect will be of great clinical importance, yet it seems that it cannot be an artefact, and so oestrone must be judged to improve sleep in perimenopausal women.

Sleep is regulated by the brain, and there are several ways in which oestrogens may influence the activity of the brain. Since oestrogen receptors have been located in many areas of the brain (Stumpf, 1971; Pfaff and Keiner, 1973) the effect of oestrogen on sleep may be due to a direct action on the brain. There is

also evidence that oestrogens can influence the metabolism of the neurotransmitters e.g. by changing the level of the precursor of serotonin, tryptophan, in plasma, oestrogens could change the metabolism of serotonin in the brain. Various workers have reported that the rate of production or the concentration of serotonin in the brain depends at least partly on the concentration of free plasma tryptophan (Fernstrom and Wurtman, 1971; Knott and Curzon, 1972; Gessa and Tagliamonte, 1974), although there is some conflicting evidence in that Fernstrom et al (1976) have recently reported that total plasma tryptophan is the controlling factor. In my study I found a high positive correlation between nocturnal plasma oestrogen and free plasma tryptophan levels in perimenopausal women, and both Aylward (1973, 1976) and Coppen and Wood (1978) have reported that oestrogen treatment leads to an increase in free plasma tryptophan concentration in menopausal women, and this suggests that oestrogen influences cerebral serotonin metabolism. Jouvett (1969, 1972) has postulated that cerebral serotonin is responsible for the maintenance of sleep, since in animal studies surgical ablation of the serotonergic neurons in the mesencephalic and pontine raphe systems leads to insomnia, and inhibition of serotonin synthesis by p-chlorophenylalanine leads to severe insomnia, which can be reversed by giving the serotonin precursor 5 hydroxyphenylalanine. Other workers have questioned the validity of these results, and Ross and Trulson (1976) pointed out that in

operating on the serotoninergetic nuclei, fibres of passage or non-serotoninergetic nuclei may have been damaged and this may have been the cause of the sleep disturbance. The insomnia produced in animals by p-chlorphenylalanine has been shown to be transient, lasting only a few days, even though the synthesis of serotonin remains suppressed (Dement et al. 1972; Ross and Trulson, 1976), and this observation led Ross and Trulson to suggest that the insomnia caused by this drug may be due to toxic or irritative effects other than the depletion of serotonin. They also observed that the behaviour of animals treated with p-chlorphenylalanine suggested a hyperresponsivity to sensory events rather than insomnia.

Breuer et al (1978) found that oestrogen influences the metabolism of catecholamines in the rat brain. They found that the activity of the enzyme catechol-O-methyl transferase (COMT) in the brain was highest in normal female rats, but was decreased by ovariectomy. This enzyme is concerned with the first step of the breakdown of noradrenaline on release from the nerve endings, methylation from noradrenaline to normetanephrine. These workers went on to study the effect of exogenous oestrogens, and were surprised to find that the administration of oestradiol-17 β to ovariectomized rats caused a further decrease in the production of the methylated metabolites of noradrenaline in rat brain. The authors inferred that oestradiol has a direct effect on the methylation of

noradrenaline, but that the mode of action could be reduction of the availability of the cofactor of COMT, S-adenosylmethionine, or by increasing the uptake of noradrenaline by the cells, or by competition of the catechol oestrogens for the enzyme COMT. There is some evidence to support the second possibility, since Endersby and Wilson (1974) found that in ovariectomized rats the accumulation of noradrenaline by brain slices was increased by pretreatment with oestrogens, but Breuer et al (1978) favoured the theory that the action is due to competition of the oestrogen metabolites, the catechol oestrogens, for COMT, since they had found that in vitro the catechol oestrogens had a higher affinity for this enzyme than the catecholamines (Breuer and Köster, 1974).

There is evidence that oestrogens may also influence the metabolism of the neurotransmitters by an inhibitory effect on the enzyme monoamine oxidase (MAO). This enzyme is widely distributed throughout the body, and is responsible for the first stage of one route of the degradation of tyramine, tryptamine, noradrenaline, adrenaline, dopamine, and serotonin. Klaiber et al (1971) reported that plasma MAO activity is inversely related to plasma oestrogen levels during the menstrual cycle, and is highest in women with low oestrogen levels, e.g. after the menopause and in women with amenorrhoea, and in a later paper (Klaiber et al, 1976) they reported that oestrogen administration decreased plasma MAO activity. There is some evidence that this is not merely a peripheral

effect, as Kobayashi et al (1966) found that ovariectomy increased MAO activity in the rat hypothalamus, and administration of exogenous oestrogens caused the activity to decrease again. It seems therefore that oestrogens have a complex action on brain metabolism, influencing several neurotransmitter systems as well as acting directly on the brain. However, the relationship between oestrogens and brain metabolism and the neurochemical basis of sleep are incompletely understood, so it is not yet possible to formulate a theory of how oestrogens affect the sleep of menopausal women by their action on the brain.

It is unlikely that the greater improvement in sleep experienced by the oestrone group is due to changes in the number of hot flushes, or in mood or anxiety, since the two groups showed similar changes in all of these symptoms. One possible cause for the change in sleep pattern on oestrogens which was not investigated in this study is change in weight. Crisp and Stonehill (1976) found that weight increase was associated with longer and less broken sleep, and weight loss with shorter and more broken sleep, and oestrogens are anabolic hormones, so they may have caused a weight increase in the oestrone group. Notelovitz (1975) found that one year's treatment with oestrogen did not cause weight gain, but he used a smaller dose of oestrogen, administered cyclically, so our studies are not comparable. Depression too can be associated with weight change, either increase or decrease,

and as the depression improves the appetite returns to normal, so mood changes may have caused weight changes in either group in my study. In retrospect, it would have been advisable to weigh the patients in my study. The last three patients in each group were weighed at the start and end of the baseline period, and at the end of the study, and I found that one patient in the placebo group lost 5 lb and another 1 lb during the baseline period, but the weights of the other patients were unchanged. During the two treatment months, one patient in the oestrone group gained 3 lb and another gained 1 lb, and one patient in the placebo group gained 13 lb, which shows that patients in both groups may have had weight changes, but the numbers are so small that it would be wrong to extrapolate these results to the rest of the patients.

PSYCHOLOGICAL SYMPTOMS

None of the patients in my study had psychotic symptoms such as delusions or hallucinations, and the mean scores of the two groups on the Hamilton depression scales, 16.3 and 18.2, would be considered to indicate depression of only mild or moderate severity by most workers. These mean scores are similar to those of the patients studied by Wheatley (1977), but are lower than these reported by Fedor-Freybergh (1977), whose patients had a mean score of 22 on the Hamilton depression scale.

The Hamilton Rating Scales showed a significant improvement in both depression and anxiety in the two

groups in my study. The visual analogue scales showed a similar pattern, but no significant changes. There was a significant correlation between the Hamilton depression scale score and the visual analogue scale of mood score at the start of the study and at weeks 10 and 14 ($r = -0.53, -0.45, -0.49$; $p < 0.01$) but the correlation was not significant at week 6 ($r = -0.10$). These correlations are inverse because a lessening in the severity of the depression was represented by a decrease in the Hamilton depression scale score and an increase in the visual analogue scale score. They are lower than the correlations between Hamilton depression rating scale scores and visual analogue scale of depression scores reported by Zealley and Aitken (1969), since they found the correlation coefficient to be 0.79 in depressed in-patients, but they also found that the correlation fell to -0.06 on recovery, suggesting that the relationship may vary with the severity of the depression, and that the lower correlation between the scales used in my study may be due to the patients being less depressed. The difference between Hamilton depression rating scales and visual analogue scales may be part due to their measuring different things, as the visual analogue scale measures only mood, but the Hamilton scale is heavily weighted towards the somatic symptoms accompanying depression, many of which are common menopausal symptoms even in the absence of depression.

Although Hamilton anxiety rating scales and visual analogue scales of anxiety showed a similar pattern of change, there were no significant correlations between either the scores or changes in score of the two scales. Again, it is likely that the two scales are measuring different parameters, since the visual analogue measures subjective anxiety, and the Hamilton anxiety rating scale is intended for measuring the severity of anxiety neurosis, and includes the physical concomitants of anxiety.

Neither Hamilton rating scales nor visual analogue scales showed any difference between the two groups of patients. This is unlikely to be due to inadequacy of the scales, since other workers have used the Hamilton depression rating scale and have found them to be sufficiently sensitive to show a difference between oestrogen and placebo treated groups (Aylward, 1973, 1976; Fedor-Freybergh, 1977). Campbell reported a significant effect of oestrogen on anxiety in menopausal women, measured by visual analogue scales, so it seems that this rating scale too is sufficiently sensitive to show changes. However, the numbers in my study are small, and it would have been possible only to show a very large difference between the two treatment groups using this number of patients.

My results showed a very marked placebo effect on symptoms of anxiety and depression in menopausal women, and this effect was so great that at the end of the baseline period neither the oestrone group nor the placebo

group were anxious or depressed. Their scores on the Hamilton rating scales at this time were so low that it would be difficult to show much improvement, and it is thus not surprising that I did not find oestrogen to be significantly more effective than placebo in relieving anxiety and depression. This improvement persisted for the duration of the study in both groups.

Many workers have commented on the marked and prolonged placebo effect on menopausal symptoms (Pratt and Thomas, 1937; Donovan, 1951; Kupperman et al, 1959; Utian, 1972a & b; Clayden et al, 1974; Coope et al, 1975; Campbell, 1976b; Strickler et al, 1977). Pratt and Thomas (1937) compared oestrogens given either orally or by injection with placebo tablets, placebo injections, and phenobarbitone tablets in 100 menopausal women, and found that physical and psychological symptoms improved to a similar degree regardless of which treatment was given. Utian (1972a) reported that oestrogen had only a placebo effect on depression occurring after oophorectomy in 85 women, but in a later study (Utian 1972b) he reported that both oestrogen and placebo had a 'mental tonic' effect on 50 oophorectomized women. This second study was a cross-over trial, and he found that the sense of well being diminished after the cross over in women who were given placebo after oestrogen treatment. George et al (1973) failed to replicate this in a double-blind cross-over study of the effect of conjugated equine oestrogens on 13 oophorectomized women, and concluded

that the mental tonic effect must be dose related, since they had used a smaller dose than Utian. George's study has been criticised by Hawkins and Polakow (1974) on the grounds that the numbers studied were too small to demonstrate a statistically significant difference, so this is another possible cause for the difference between his results and those of Utian (1972b). Rauramo et al (1976) also failed to show that oestrogen was more effective than placebo in relieving anxiety or depression in oophorectomized women, and Campbell (1976b) also failed to show that oestrogen was significantly more effective than placebo in relieving depression in his cross-over studies on 64 women with severe menopausal symptoms and 56 women with milder symptoms. He commented on the marked placebo effect, which lasted for six months in many cases and found that both oestrogen and placebo produced a significant improvement in depression, and although oestrogen had a greater effect than placebo, the difference between them was not significant. He concluded that oestrogen was more effective than placebo, but that the rating scale used, the Beck self rating scale, was not sufficiently sensitive to demonstrate this.

Strickler et al (1977) also found a marked placebo effect, with no significant difference between oestrogen and placebo treatment, in their cross-over study of the effect of conjugated equine oestrogens on climacteric symptoms in 20 women. They attributed the marked placebo effect to the sympathetic interest of a health

care worker, since they had controlled for physician-dependence by arranging for patients to see a different doctor at each visit, but the health care worker saw the patients at every visit. This agrees with the opinion of Donovan (1951) who relieved symptoms in the majority of patients by history-taking alone, and in the remainder by a placebo injection. He stated that the most important factor in symptomatic relief is a good doctor-patient relationship, in which the patients could discuss their symptoms freely, and if this is so, the placebo effect in my study could have been due to the attention received by the patients, since they spent an hour a week talking to myself or my assistant while the electrodes were being attached for sleep recording, and had breakfast with us the next morning.

Aylward reported that oestrogen was more effective than placebo in relieving depression in oophorectomized women (Aylward, 1973) and in postmenopausal women (Aylward, 1976). In his first study he related depression to low free plasma tryptophan levels, and observed that oestrogen treatment both relieved depression and raised the free plasma tryptophan levels. He reported a significant correlation between changes in free plasma tryptophan levels and change in the severity of depression, but since no information was given about the actual scores on the Hamilton depression rating scale, it is not clear how depressed the patients were, nor how greatly they improved. In his study of the effect of oestrogen treatment on

postmenopausal women, he treated all patients with placebo before the start of the study, and entered only those who failed to respond to placebo treatment. The 65 patients who did not respond to placebo were randomly allocated to either placebo treatment or treatment with piperazine oestrone sulphate, and he found that the score of the oestrogen treated patients on the Hamilton depression rating scale fell, while the placebo-treated patients became more depressed, and showed an increase in their scores, but as his results are expressed only as % change it is impossible to tell how severely depressed the patients were, or how significant were the differences between the two groups.

Fedor-Freybergh (1977) also found that oestrogen was significantly better than placebo in relieving depression. In his study, 21 postmenopausal women with symptoms of depression were given a supply of tablets, told that this treatment would make them better, and given an appointment for three months time. Ten cases in this study were given placebo, and 11 given oestrogen. At the end of the three months, he found that the patients on placebo had deteriorated, and those on oestrogen improved significantly. In his study there was no placebo effect, and this may be due to the limited number of interviews, which prevented the development of a supportive relationship with any member of staff of the clinic. It seems, then, that attention and supportive interviews are very effective in relieving depression and anxiety in postmenopausal

women, and that the placebo effect can last for as long as six months (Campbell, 1976b). Two of the studies which claimed that oestrogen treatment is more effective than placebo in relieving depression in postmenopausal women have either eliminated placebo responders from the study (Aylward, 1976) or reduced contact between patients and staff (Fedor-Freybergh, 1977), so it is possible that oestrogen has an antidepressant effect on some patients, or that this effect is masked by the placebo effect when the patient receives more attention. Overall it would suggest that even if oestrogen is better than placebo for symptom relief, its contribution is probably small in clinical practice compared with that of the doctor-patient relationship.

The main purpose of my study was to investigate the effect of oestrogen treatment on sleep disturbance, and in view of the small numbers studied, it is not surprising that oestrogen was not found to be more effective than placebo in relieving psychological symptoms. It did show, however, that the improvement in sleep in the oestrone group is not likely to have been due to lessening of anxiety or depression, since the groups showed a similar improvement in these symptoms as rated by both subjective and observer ratings.

HOT FLUSHES

In both the oestrone and the placebo group there was a decrease in the frequency and severity of hot flushes. There was a very high correlation between the number of hot flushes and the severity rating, which suggests that either the number of hot flushes was the main factor to be taken into account when the severity rating was completed, or the number and severity of the hot flushes changed in parallel. It should also be borne in mind that the number and severity of hot flushes were recorded at the same time each day, so the second rating may have been influenced by the first.

My study failed to show that oestrogen was more effective than placebo in relieving hot flushes, but since the number of patients in each group was relatively small, this result should be interpreted with caution. Pratt and Thomas (1937) in their study of 100 patients, also failed to show that oestrogen was more effective than placebo, as did Coope et al (1975) in the first three months of their cross-over study, before the cross-over period.

The placebo effect on hot flushes has been known for some time, and was described by Donovan (1951), Kupperman et al (1959), Clayden et al (1974), Coope et al (1975), and Campbell (1976b), but as yet we know little about this effect. Greenblatt et al (1950) suggested that women who responded to placebo treatment were psycho-neurotics, and Lauritzen (1973) that they did not have

true menopausal symptoms, but since the symptoms of placebo responders and non-responders are the same this theory is doubtful. Campbell (1976b) found that the placebo effect could last four six months, and in his cross-over studies found that the effect of placebo treatment was significant in patients with mild symptoms ($p < 0.05$), and short of significance in patients with severe symptoms, but that in both groups oestrogen was significantly more effective than placebo in relieving hot flushes. Many other cross-over studies have shown oestrogen to be more effective than placebo in the treatment of hot flushes, e.g. Greenblatt et al (1950), Kupperman et al (1953), Martin et al (1971), Lauritzen (1973), Utian (1972a), and Coope et al (1975), but when the evidence for a relationship between oestrogen and hot flushes was reviewed by Mulley and Mitchell (1976a), they concluded that there was no evidence that oestrogen was significantly more effective than placebo. Utian (1976) and Coope (1976) disagreed with this view, and Sturdee and Gustafson (1976) pointed out that Mulley and Mitchell (1976a) had reviewed only two studies, those of Pratt and Thomas (1937) and Coope et al (1975). Mulley and Mitchell (1976b) replied that they had been unable to find any other well conducted double-blind cross-over studies, and discounted the studies mentioned by Sturdee and Gustafson (1976) on the grounds that the study of Greenblatt et al (1950) could not have been double-blind because vaginal cytology was carried out on the patients

during treatment, and the studies of Kupperman et al (1959), Martin et al (1971) and Lauritzen (1973) did not include a cross-over period with placebo. However, Pratt and Thomas (1937) make no mention of cross-over of treatments, and while Coope et al (1975) found that there was no difference between placebo and oestrogen in the first part of their study, they found oestrogen to be significantly more effective after the cross-over. This controversy over the value of oestrogen treatment can only be resolved by research into the cause of hot flushes to enable us to understand the reasons for these conflicting results, and a large, long-term study to compare oestrogen and placebo treatment.

Campbell (1976b) found that insomnia was relieved by oestrogen treatment only in women with vasomotor symptoms, but there were insufficient patients without hot flushes in my study (one in the placebo group and two in the oestrone group) to test this hypothesis. There was no correlation in my study between the mean hot flush count or severity rating and either the amount of intervening wakefulness or sleep duration in the three periods of the study, nor was there a significant correlation between the changes in these parameters. Since the oestrone and placebo groups showed similar changes in the number and severity of hot flushes, the improvement in sleep in the oestrone group is not likely to have been due to a change in vasomotor symptoms.

Campbell (1976b) also described a "domino" effect, in that when one symptom improved, many other complaints were relieved at the same time, and by comparing patients with and without vasomotor symptoms, he concluded that it was the abolition of hot flushes and vaginal atrophy which caused the improvement in the other, unrelated symptoms. In my study too measures of mood, anxiety, sleep quality, and hot flushes showed that these improved in parallel, but it was not possible to show whether the improvement in one symptom led to the change in the others. Since anxiety is one of the factors known to worsen hot flushes, it is possible that reduction in the anxiety level reduced the physiological arousal and thus lessened the number of hot flushes, rather than vice versa.

NEUROENDOCRINE STUDIES

Oestrogens

My patients showed rapid, episodic variations in their plasma levels of both oestrone and oestradiol, and since the coefficient of variation of the assay was 14% it is unlikely that this finding was due entirely to unreliability of the assay method. My finding of erratic variations in the plasma levels of both oestrone and oestradiol in perimenopausal women confirms the results of Jacobs et al (1977) and Hutton et al (1978), and like them I could find no evidence of a diurnal rhythm in the levels of either hormone. Their studies were similar

to mine in that they took blood samples every 20 or 30 minutes for several hours from their patients. Campbell (1976a) also noted fluctuations in both oestrone and oestradiol levels in menopausal women, but he found a diurnal variation in plasma oestrone levels, with the lowest levels occurring between 18.00 and 02.00.

Vermeulen (1976) also reported a diurnal variation in plasma oestrone levels, with the nadir occurring between midnight and 04.00, but these authors took blood samples only every two hours from a small number of patients, and the differences in their results may have been due to the different frequency of taking blood samples.

There was no clear relationship between the changes in oestrone and oestradiol levels during the night in individual patients, but there was a significant positive correlation between mean oestrone and oestradiol levels when we consider all twelve patients on the first blood night, and also the patients in the placebo group on the second blood night. Campbell (1976a) observed that two of the patients in his study who had high oestrone levels also had high oestradiol levels, but other than this he found no relationship between plasma levels of the two hormones, and Hutton et al (1978) in their extensive study found no correlation between mean oestrone and mean oestradiol levels.

The mean oestrone levels of the patients in my study were low, but were comparable with the lower levels found during the menstrual cycle. The mean oestradiol levels

in many cases were lower than those expected during the menstrual cycle, but in the four patients who had amenorrhoea of less than one years duration the mean oestradiol levels were compatible with those of the early follicular phase of the menstrual cycle. There was a significant inverse relationship between the mean oestradiol level and the duration of amenorrhoea when the levels in the patients on the first blood night were considered, but the relationship between the mean oestrone levels and duration of amenorrhoea was short of significance. The levels of both oestrone and oestradiol were highest in the patients with amenorrhoea for less than one year. Chakravarti et al (1976) also found that oestrogen levels changed with time after the menopause. They found that the levels of both oestrone and oestradiol fell progressively after the menopause, but while the oestrone levels remained low, the oestradiol levels seemed to rise again after 20 years. However, Hutton et al (1978) could find no relationship between either age or duration of amenorrhoea and oestrone or oestradiol levels. It is difficult to see why my results should differ from those of Hutton, since we used a similar sampling schedule and patients of similar ages, though the duration of amenorrhoea experienced by his patients ranged from 0.4 to 15 years, and was therefore wider than the range in my study.

It can be seen from Table 1 that the mean oestrone and oestradiol levels of menopausal women reported by

various workers vary widely. The mean plasma oestrone and oestradiol of my patients on the first blood night, when all were receiving placebo, are similar to the mean levels reported by Campbell (1976a) and by Hutton et al (1978), but are higher than the values reported by many other workers. The difference between my results and those of other workers may be due to differences in assay methods, sampling schedules, or populations studied. In my study and that of Hutton et al (1978), blood samples were taken every 20 or 30 minutes, while Campbell (1976a) and Vermeulen (1976) took samples every two hours and most other workers took only a single sample from each patient. In view of the wide and rapid fluctuation in oestrogen levels in menopausal women, both Campbell (1976a) and Jacobs et al (1977) have stated that single sample studies are inadequate in assessing their oestrogen status, and this may be the cause of the differences reported by the various authors. They have also studied different age groups, as can be seen from Table 1, and this too may have contributed to the differences between studies. As previously stated, Chakravarti et al (1976) found that oestrogen levels varied with age after the menopause, and although Hutton et al (1978) did not confirm this finding they used a much more limited age range, and this may be the cause of their different results. It is not likely that the differences in the mean oestrogen levels reported by the different authors were due to the inclusion of women who had undergone oophorectomy, since Rader et al

(1973) found that the oestrogen levels of oophorectomized women were the same as the levels of women who had undergone a physiological menopause.

The oestrone:oestradiol ratio of the patients in my study was greater than 1 in all cases, as would be expected in postmenopausal women. It varied considerably between patients, but there was no significant relationship between the ratio and the duration of amenorrhoea experienced.

In the study of Chakravarti et al (1976) the oestrone:oestradiol ratio was highest in the first year after the menopause, and after 10 years was actually less than 1. None of the patients in my study had more than eight years amenorrhoea, so our results are not inconsistent. The oestrone:oestradiol ratio in my patients was in most cases higher than that reported by Jacobs et al (1977), who found a mean ratio of 1.6:1, and Chakravarti et al (1976) and Hutton et al (1978), who found 1.7:1. Others too have found a higher oestrone:oestradiol ratio, ranging from Vermeulen's ratio of 2.4:1 to Baird and Guevara, (1969) who found a ratio of 5.5:1. Before the menopause the ratio of oestrone to oestradiol is less than one, and the increase in the ratio after the menopause indicates that the fall in oestradiol levels is greater than that in oestrone.

When comparing oestrogen levels on the two nights, it is surprising to find so much variation in the mean oestrogen levels in the placebo group. One patient showed a decrease in both oestrone and oestradiol levels,

another an increase in oestrone levels, and a third an increase in oestradiol levels. The first patient had amenorrhoea for only six months, and observed some slight bleeding 10 days before the second blood night, and the second patient had amenorrhoea for four months, so both may still have been undergoing the menopausal transition, as described by Sherman et al (1976). These workers reported a variable potential for hormone secretion in the residual ovarian follicles of older women, leading to erratic fluctuations in oestrogen levels, and irregular bleeding, and they observed that there could be as long as five months between periods in this transitional phase. This would not account for the increased oestradiol levels of the third patient, since she had eight years amenorrhoea.

Coope (1976) suggested that the placebo response shown by menopausal women might be due to an increase in the secretion of endogenous oestrogens, but my results do not support this theory. The placebo group showed little mean change in the levels of either oestrone or oestradiol, and when the changes in individual patients are considered, two showed a pronounced increase in their oestrogen levels, and one a large decrease, but there was no obvious difference in the changes in hot flushes, mood, or anxiety between these three patients.

The effect of oestrogen administration on the oestrogen levels of postmenopausal women depends on the type of oestrogen, the dose, and the duration of treatment. Hutton et al (1977) found that giving 1.5 mg of piperazine

oestrone sulphate to previously untreated menopausal women causes a 4-5 fold rise in oestrone levels within six hours to a peak of approximately 36 ng/dl (1407 pmol/l), and oestradiol levels to rise 2-3 fold to 5 ng/dl (185 pmol/l). Jacobs gave 3 mg of this preparation and found that the plasma oestrone concentration increased to over 40 ng/dl (1481 pmol/l) while the oestradiol levels changed little, but he gives no further details of his results.

Anderson et al (1978) investigated the effect of giving 1.5 mg piperazine oestrone sulphate to women who had been on oestrogen treatment for some time, but had undergone a 48-hour withdrawal period before the study, and she found that the plasma oestrone concentration rose to a peak of 900 pmol/l (24.5 ng/dl) again within six hours but their oestradiol levels were unchanged, and remained at 294-367 pmol/l (8.0 - 10.0 ng/dl).

Although my patients took 1.5 mg piperazine oestrone sulphate one hour before the start of blood sampling, they did not show an increase in either oestrone or oestradiol levels to a peak level, but showed in all cases erratic fluctuations in the levels of both hormones, with a series of peaks and troughs. Again, these variations are too wide to be due entirely to unreliability of the assay method. Their peak plasma oestrone concentration ranged from 511.0 pmol/l (13.8 ng/dl) to 2085.2 pmol/l (56.3 ng/dl), with the average value being 1326.0 pmol/l (35.8 ng/dl). Although there was considerable variation between patients, the average is slightly lower than the

peak value reported by Jacobs in his study of the effect of this dose on untreated women, but it is higher than the levels reported by Hutton and Anderson, who used only half the daily dose received by my patients. The peak plasma oestradiol concentrations of my patients ranged from 231.6 pmol/l (6.3 ng/dl) to 415.0 pmol/l (11.3 ng/dl), with the average value being 338.2 pmol/l (9.2 ng/dl). This average value is higher than the peak oestradiol concentration reported by Hutton, but similar to that of Anderson.

The difference in our results may be due to irregular absorption from the gut in my patients, caused perhaps by taking the tablet at night just before sleep. Little is known of the metabolism of oestrogen in patients on long term oestrogen treatment, so it is difficult to think of any other cause for the episodic changes in oestrone and oestradiol levels in the patients who had received four weeks oestrogen treatment. The difference in peak levels could also be due to our patients having different lengths of treatment, since Jacobs et al (1977) reported that at the start of treatment the patients had very high plasma oestrone concentrations, while oestradiol levels rose only gradually, but after three weeks treatment, the ingestion of oestrogen tablets produced little change in either oestrone or oestradiol levels. They give no data to support this statement, but it can be seen from comparing the results of Hutton et al (1977) with those of Anderson et al (1978) that Anderson's patients, who had only undergone 48 hours withdrawal from oestrogen

treatment, showed lower peak levels and had higher oestradiol levels than the patient reported by Hutton, who was previously untreated. Cooper et al (1974) and Daw (1975) investigated the effect of treatment with piperazine oestrone sulphate 3 mg/day on the plasma oestradiol concentration of oophorectomized women, and found that oestradiol levels rose to a peak in the early weeks of treatment, then after a month stabilised at approximately 3-4 times the baseline level.

Because of the small numbers of patients studied on oestrogen treatment, the results of the changes in their oestrogen level should be interpreted with caution. The mean oestrone levels increased in all patients after four weeks of oestrogen treatment, as would be expected, but the magnitude of this increase varied between patients. Two of the patients showed only small increases, but the others had mean levels of 736 pmol/l (19.9 ng/dl) and 718 pmol/l (19.4 ng/dl), levels which are similar to or slightly higher than the highest plasma oestrone concentrations found during the menstrual cycle by Emmert et al (1972) and Judd (1976). Oestrogen treatment had no consistent effect on the plasma oestradiol concentrations of my patients as two patients showed an increase, one a decrease, and one little change in their mean plasma oestradiol levels. The patient who showed the greatest increase in her mean plasma oestrone level showed the greatest increase in her oestradiol level, while the

patient with the smallest increase in her plasma oestrogen concentration showed a decrease in her mean plasma oestradiol level. The patients who showed a decrease or only a small increase in their plasma oestradiol levels may not have been taking their tablets regularly, as compliance is frequently low in patients who are given a prolonged course of treatment, but the patient who showed a decrease in her oestradiol levels had been taking antibiotic treatment for a urinary tract infection for 10 days before the second blood night and this may have affected the absorption of the oestrogen tablet, as has been reported for the oral contraceptive pill.

Most of the workers who have investigated the effect of a prolonged course of oestrogen treatment have taken only single blood samples from each patient, so the levels they have found will depend on the oestrogen used, the dose, and possibly the time since ingestion of the last tablet. Aylward (1976) studied the effect of treatment with piperazine oestrone sulphate 3 mg/day on postmenopausal women, and found that after one month their plasma oestrone concentration had increased by 600-1000%, and oestradiol by 50-400%. This is much greater than the increase in the mean oestrone level in my patients, who showed increases ranging from 30-200%, and in my study the change in plasma oestradiol levels varied from a decrease of 60% to an increase of 580%. Unfortunately, Aylward gives only a % change, and not the absolute concentrations

of the hormones, so it is not possible to tell whether my patients had similar oestrogen levels to his either before or after treatment.

Cooper et al (1974) and Daw (1975) reported the change in plasma oestradiol concentration in oophorectomized women treated with piperazine oestrone sulphate 3 mg/day. Before treatment, the plasma oestradiol levels of his patients were similar to the mean plasma oestradiol levels of my patients on placebo, but at the end of one month his patients had plasma oestradiol concentrations of 9-10 ng/dl (331-588 pmol/l), a considerably greater increase than that shown by my patients. Our studies differed in that Cooper and Daw took only single samples from each patient at weekly intervals, and their patients were oophorectomized women, and this may account for the difference in our results. Cooper also correlated symptomatic relief with a rise in plasma oestradiol concentration to above 4 ng/dl (148 pmol/l), but my study does not confirm this finding, since the placebo group patients showed as great a subjective improvement in their symptoms as the oestrone group, while their oestradiol levels remained below 148 pmol/l in all except one case.

Lind et al (1978) studied the changes in plasma hormone levels of nine postmenopausal women on cyclic oestrogen treatment (4 on piperazine oestrone sulphate 1.5 mg/day, 2 on equine oestrogens 1.25 mg/day, 3 on oestradiol valerate 2 mg/day), and took a fasting blood

sample at the end of each 20 day course of treatment for six months. He found that their mean plasma oestrone concentration increased by 64% to 596 pmol/l (16 ng/dl), and their mean oestradiol by 470% to 357 pmol/l (9.7 ng/dl). Although he used smaller doses than were used in my study, the increases in plasma oestrone and oestradiol in his patients were greater than the mean changes in mine. This may be due to the different oestrogens used in his study, but is more likely to be due to selection of patients, since the cases reported by Lind were selected because of their high oestrogen levels on treatment to investigate the relationship between changes in oestrogen and prolactin levels.

Hutton et al (1977), Jacobs et al (1977) and Anderson et al (1978) reported that the effect of oestradiol valerate 2 mg/day on plasma oestrone and oestradiol did not differ significantly from that of piperazine oestrone sulphate 1.5 mg/day, so it is surprising that Larsson-Cohn et al (1977) found that treatment with oestradiol valerate 2 mg/day caused a greater increase in plasma oestrone than was found in my patients, who received 3 mg/day piperazine oestrone sulphate. The mean plasma oestrone concentration of their patients increased by 587% to 810 pmol/l (22 ng/dl), which is much greater than the increase shown by my patients. Their mean plasma oestradiol concentration increased by 235% to 191 pmol/l (5.2 ng/dl), and although this is lower than the mean

oestradiol level of the two patients in my study whose oestradiol level increased markedly, and is close to the average of the mean oestradiol levels of my four patients, it should be noted that Hutton et al (1977) and Anderson et al (1978) found this dose to be equivalent to 1.5 mg piperazine sulphate, when my patients were on twice this dose daily. However, Hutton compared the effects only on patients on the first day of treatment, and Anderson on patients who had undergone 48 hours withdrawal from their oestrogen therapy, so it is not conclusively proven that long-term treatment with piperazine oestrone sulphate and oestradiol valerate has the same effect on plasma oestrogen concentrations, and the difference in our results may be due to the different types of oestrogen treatment used.

Jacobs et al (1977) remarked that oestrogen treatment is not physiological because it does not restore the oestrone:oestradiol ratio to that of premenopausal women, and my results support this view. Although the ratio increased in two patients and decreased in two in my study, it was not lower than one in any patient, and if the mean values are considered in the four patients in the oestrone group who completed both blood nights, the ratio was unchanged. On the first night, when the patients were on placebo, the mean ratio was 3.6:1, and on the second night, after a month's oestrogen treatment, the ratio was 3.5:1. Lind et al (1978) also found that oestrogen treatment produced little change in the

oestrone:oestradiol ratio, but Jacobs et al (1977) found that it increased. Jacobs gives no details of his results, but since he found that oestrone levels rose before oestradiol levels, it is possible that he was referring to women who had just started oestrogen treatment. It is interesting to note that the mean oestrone:oestradiol ratio of individual patients in the placebo group in my study also varied considerably between the two nights studied, showing an increase in three cases and a fall in three cases, though the group mean was little changed, being 2.9:1 on the first night and 2.6:1 on the second.

I could find no relationship between changes in hormone levels and changes in sleep stage, nor was there any correlation between mean hormone concentrations and sleep duration or the amount of any sleep stage or intervening wakefulness. This agrees with the results of Alford et al (1973), who studied the oestrogen levels during sleep of adult women. The only report of a relationship between oestrogen levels and sleep in normal subjects is that of Boyar et al (1976), in which they found a fall in oestradiol levels during sleep in pubertal girls, but since the time of puberty is unique in the changes in hormone regulation, it may be inappropriate to compare this study with studies of adult subjects.

Prolactin

In my patients, the plasma prolactin concentrations before sleep onset ranged from 0 to 300 mIU/l (0-15.0 ng/ml), with the average being 118 mIU/l (5.9 ng/ml) on the first blood night. In the placebo group the mean plasma prolactin concentration before sleep onset was lower on the second night than the first, and in the oestrone group it was higher, but the numbers studied were too small for this difference to be significant, and the level may have been affected by factors such as the stress of having an intravenous catheter inserted, since stress is known to cause a rapid increase in prolactin secretion. The average plasma prolactin concentration before sleep on the first night was lower than the mean prolactin level of menopausal women reported by Lind et al (1978), which was 166 mIU/l, and also lower than the mean level reported by Vekemans and Robyn (1975a) for women in this age range, but these authors took blood samples early in the day, while mine were taken after 10 p.m., so the difference in our results may be due to a diurnal variation during waking hours.

Studies of the effect of oestrogen treatment on prolactin levels during the daytime have also had conflicting results. Delvoye et al (1972) found that a combination of oestrone and oestradiol reduced plasma prolactin levels in postmenopausal women after a three week course of treatment, but after a further three weeks of oestrogen treatment the levels were the same as those

found before starting treatment. Robyn and Vekemans (1976) found that administration of ethinyl oestradiol 50 µg/day caused a significant increase in the plasma prolactin concentration of postmenopausal women after ten days, but Lind et al (1978) found that cyclic treatment with a variety of oestrogens caused marked increases in the plasma oestrogen levels of nine postmenopausal women, but had no effect on their plasma prolactin. The different results may be due to the various workers using different oestrogens or testing the effect after different lengths of treatment, but since they studied only daytime levels it is not surprising if their results differ from mine.

My patients all showed an increase in the secretion of prolactin after sleep onset, confirming the report of Rozenowicz et al (1973) that the pattern of secretion of prolactin is unchanged after the menopause. The pattern of secretion of my patients was similar to that observed by Sassin et al (1972) and Parker et al (1974) in their studies of younger people. Like Sassin, I found that the increase in prolactin secretion began in most cases within 60-90 mins. of sleep onset, and took longer than 120 mins. in only two cases in my study. The increased secretion lasted for 6-8 hours, until the end of the sleep period, and since the secretion of prolactin is episodic, there were a series of peaks in plasma prolactin concentration during the night. The magnitude of the increase, and the peak values observed, varied widely between patients

in my study, and although there was some variation in the peak and mean values between nights in the same subject, the overall pattern was consistent. Sassin et al (1973) also remarked on the variability between subjects, and this may in part account for the differences in the peak prolactin levels reported by various authors, though there may also have been differences in the sensitivity of the assay method in different laboratories. Sassin et al (1972) observed peak values of 50 ng/ml, and Parker et al (1974) of 35 ng/ml, while Rosencweig et al (1973) reported peaks of 200 mU/ml in postmenopausal women. In my study, the mean of the peak prolactin concentrations was similar to the peak levels reported by Sassin and Parker, but the range of individual values was very wide. Sassin et al (1972) reported that the peaks of prolactin grew progressively higher during the sleep period, but this was not the case in most of the patients in my study, nor in the study of Parker et al (1974). Parker found that the peaks of prolactin secretion occurred just after REM periods, but other workers have not reported this, and it was not found in my study. The only relationship found between prolactin and sleep in my study was the correlation between mean nocturnal plasma prolactin concentration and the amount of slow wave sleep, and this was observed only on the first night, and has not been reported by other workers, so may be due to chance.

There was no significant correlation between mean prolactin levels and mean oestrone, oestradiol, or total plasma oestrogen concentrations, nor between the changes in prolactin and oestrogen concentrations during the night, and the mean and peak prolactin levels were unrelated to either age or duration of amenorrhoea. Because of the small numbers of patients studied while on oestrogen treatment, and the variability of the changes in hormone levels, no firm conclusions can be drawn from my results about the effect of oestrogen treatment on nocturnal prolactin secretion. Two of the patients, Cases 8 and 9, showed little change in either the levels or the pattern of secretion of prolactin while on oestrogen treatment, but also showed only small changes in their oestrogen levels. The two patients who showed the greatest change in their plasma oestrogen concentrations, Cases 7 and 10, also showed changes in prolactin secretion. Case 7 had a very high mean and peak prolactin concentrations on the first blood night, when on placebo, and differed markedly from the other patients on this night. The cause of her high prolactin levels is not known, since she was a healthy though slightly overweight woman, and had no significant medical history. She was not on the oral contraceptive pill, or any other medication, and did not report any unusual stress or exercise, so the cause of her high prolactin levels remains unknown. When on oestrogen treatment, she showed an earlier increase in her plasma prolactin concentration, and higher mean

and peak values than found on the first night. Case 10 also showed a change in prolactin secretion when on oestrogen treatment, with an earlier increase and a series of low peaks rather than a single high one. These results suggest that the nocturnal pattern of secretion of prolactin may be altered by a major increase in oestrogen levels, but because of the small number of patients, and the variability between nights and subjects even on placebo, this is not certain and a much larger study would be necessary to test this theory.

Only Copinschi et al (1975) and Vekemans and Robyn (1975b) have studied the effect of oestrogen treatment on the circadian changes in prolactin secretion, and both have studied young women. Copinschi found that the oral contraceptive pill had no effect on the diurnal changes in prolactin secretion, but he took blood samples only every four hours in 7 subjects. Vekemans and Robyn reported that treatment with ethinyl oestradiol in a dose of 400 $\mu\text{g}/\text{day}$ for 10 days changed the pattern of prolactin secretion in five young women, in that the increase in secretion started in the afternoon instead of after sleep onset, and the amplitude of the nocturnal peak was decreased. Since the patients in my study were older, and had been treated with a different oestrogen for a longer period, it may not be comparable with those of Copinschi or Vekemans and Robyn, and there were also differences in the sampling schedules of our studies, which could cause differences in results.

Tryptophan

The mean total plasma tryptophan concentrations of my patients are similar to those of other workers. I found that there were rapid variations in total tryptophan concentration during the night in all of my patients, as did Chen et al (1974) in their study of nocturnal plasma tryptophan levels in young women. I also found a diurnal variation in total tryptophan, with the lowest levels occurring between 2 a.m. and 5 a.m., which confirms the findings of Fernstrom and Wurtman (1974) and Niskanen et al (1976), but disagrees with the results of Chen et al (1974) and Young et al (1969). Chen found that total plasma tryptophan concentrations fell throughout the night in young women, but it is not clear from his paper how often he took blood samples, and this makes it difficult to evaluate his results. Young found that the total plasma tryptophan levels of young men rose between 1 a.m. and 8 a.m. and showed that the diurnal pattern was related to dietary pattern since it could be abolished by changing the frequency of meals, so it is possible that the different nocturnal plasma tryptophan levels are due to differences in diet. The effect of the diet on plasma tryptophan levels is complex, and Wurtman et al (1968) found that the diurnal variation persisted in volunteers who ate no protein for two weeks, while Marliss et al (1970) found that it could be abolished by fasting. This led Fernstrom and Wurtman (1974) to suggest that the diurnal changes in plasma tryptophan are of

nutritional origin, and may be due to the postprandial release of insulin and other hormones which modify tissue uptake of amino acids.

The free plasma tryptophan concentrations of the patients in my study are similar to those reported by Aylward (1973, 1976), Chen et al (1974), Niskanen et al (1976) Peet et al (1976), and Coppen and Wood (1978), but are lower than those reported by Riley and Shaw (1976). I found that the free plasma tryptophan concentrations also fluctuated rapidly throughout the night in my patients as did Chen et al (1974), but I could find no consistent pattern or diurnal variation, while Chen found that the free plasma tryptophan levels of his subjects fell during the night. He also reported a significant inverse correlation between mean levels of free and bound plasma tryptophan but the number of patients in my study was insufficient to give any valid results of such a relationship. When the relationship between changes in free and bound plasma tryptophan levels during the night is considered in individual cases, only one of my patients showed a significant correlation between free and bound plasma tryptophan levels, while two showed a correlation between free and total plasma tryptophan concentrations. I could find no relationship between changes in either free or total plasma tryptophan levels and changes in sleep stages, which confirms the findings of Chen et al (1974). He reported a significant inverse relationship between mean free plasma tryptophan concentration and the

amount of non-REM sleep, and a positive correlation between mean free plasma tryptophan concentration and the amount of REM sleep (Chen et al. 1974) but a subsequent, larger study failed to confirm the relationship between free plasma tryptophan and REM sleep (Chen et al, 1975). The numbers of patients in my study are insufficient to show any significant relationships between mean free and total plasma tryptophan concentrations and the amount of any sleep stage.

I have found a significant positive correlation between oestrogen levels and both level and % free plasma tryptophan. Although the correlation is significant when oestrone, total oestrogens, and level or % of free plasma tryptophan are considered, the relationship is highest between total plasma oestrogen and % free plasma tryptophan. Tryptophan circulates in plasma bound to albumin (McNenamy and Oncley, 1958) and since oestrone too can bind to albumin, and oestrogens have been shown to displace tryptophan from albumin binding in vitro (Aylward and Maddock, 1973) then this relationship is probably due to a direct action of oestrogen in displacing tryptophan from its binding sites. Aylward (1976) has also reported a significant correlation between free plasma tryptophan concentration and both oestrone and oestradiol levels in a study of 79 perimenopausal patients. This holds true for the mean levels in my three patients, though it should be noted that the numbers are too small to be significant. When the changes occurring throughout the night are

considered, then I found a significant correlation between oestrone levels and free plasma tryptophan concentrations in all three cases, but between oestradiol and free plasma tryptophan concentrations in only one case.

Aylward has postulated that this relationship between oestrogen levels and free plasma tryptophan is of aetiological significance in depression in perimenopausal women. He reported (Aylward, 1973, 1976) that depressed perimenopausal women had low free plasma tryptophan levels. Coppen et al (1972) first reported a relationship between free plasma tryptophan levels and mood in the middle aged women when they observed low free plasma tryptophan levels in depressed menopausal women compared with controls, and found that the levels returned to normal on recovery from depression. Other workers, however, have found conflicting results. Niskanen et al (1976) in a study of depressed hospital in patients of both sexes, mean age 43, found free plasma tryptophan levels to be higher in cases than in controls when both were receiving a standard diet, while Peet et al (1976) in a study of female in-patients and controls receiving a standard diet, could find no difference between cases and controls. Riley and Shaw (1976) in a study of fasting blood levels in both sexes also failed to find a difference between depressives and controls. The differences in these results may be due to dietary factors, since Coppen and Wood (1978) have demonstrated that a high protein diet can abolish the difference in

free plasma tryptophan levels between depressives and controls. Another factor in the different results may be the age group of patients studied. Most authors have included middle aged women, whose free plasma tryptophan levels fall in parallel with their oestrogen levels (Aylward, 1976). Coppen and Wood (1978) also observed a fall in free plasma tryptophan levels in perimenopausal women in the control group, though not in the depressive group, in their study.

Aylward (1973, 1976) has claimed that oestrogen treatment both improves depression and increases free plasma tryptophan levels in depressed perimenopausal women, while placebo treatment has no effect on either parameter. Coppen and Wood (1978) have also observed that oestrogen treatment increases free plasma tryptophan levels in female depressed patients, but they do not, however, give details of the age group of their patients and the cases in their study were two bipolar and one unipolar depressives all of whom were receiving lithium, but had mild residual affective symptoms. They did not find any significant difference in mood when cases treated with placebo and oestrogen were compared, but this is hardly surprising in view of the small numbers studied.

CONCLUSION

I have shown by objective measures that oestrogen treatment decreases the brokenness of sleep in perimenopausal women complaining of insomnia. This improvement in sleep was present in the first month of treatment, and was greater in the second month, but further studies would be required to determine whether this improvement persists or increases with further treatment, and whether it is reversed by withdrawal of oestrogen treatment.

I found only placebo effects on mood, anxiety, and hot flushes in my patients. This may be due to the small number of patients, and a larger study might have given different results. The patients in my study received a great deal of attention, which would enhance the placebo effect, and it is possible that oestrogen is more effective than placebo in relieving menopausal symptoms in patients who receive less attention. Further work will be required to determine the duration of the placebo effect, and since the work of Aylward (1976) suggests that some depressed women respond to oestrogen but not to placebo treatment, the difference between placebo responders and non-responders in terms of symptoms, previous history, and hormone levels should be investigated. It was surprising to find that oestrogen was no more effective than placebo in relieving hot flushes, because it is widely believed that oestrogen treatment abolishes vasomotor symptoms, and I was advised at the start of the study that it is not possible to carry out a double blind study of the

effectiveness of oestrogen therapy because of this. I was unable to tell either from the reduction in hot flushes or the side effects experienced which patients were receiving oestrogen and which placebo.

Neuroendocrine studies showed a nocturnal increase in plasma prolactin levels such as is found in younger people, but the levels of oestrone and oestradiol fluctuated widely and rapidly in all cases, with no clear diurnal rhythm or relation to sleep during the night. Unfortunately only four patients were studied after oestrogen treatment, and while all showed an increase in their nocturnal plasma oestrone levels, no consistent change in either oestradiol or prolactin was found. The effects of oestrogen treatment seem to vary with the duration of treatment, so it would be useful to investigate the effect of oestrogen treatment on a larger number of patients after various lengths of treatment to clarify the effect of oestrogen on plasma hormone levels. Tryptophan assays were carried out on only three patients and showed a high correlation between plasma oestrogen levels and the concentration of free plasma tryptophan, but the number studied was insufficient to show any relationship between their mean levels, or between mood and free plasma tryptophan concentration.

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APPENDIX I HAMILTON RATING SCALES**A. HAMILTON RATING SCALE OF DEPRESSION**

Item No.	Range of Scores	SYMPTOM
1	0-4	<u>Depressed Mood</u> Gloomy attitude, pessimism about the future Feeling of sadness Tendency to weep Sadness, etc..... 1 Occasional weeping.. 2 Frequent weeping.... 3 Extreme symptoms ... 4
2	0-4	<u>Guilt</u> Self-reproach, feels he has let people down Ideas of guilt Present illness is a punishment Delusions of guilt Hallucinations of guilt
3	0-4	<u>Suicide</u> Feels life is not worth living Wishes he were dead Suicidal ideas Attempts at suicide
4	0-2	<u>Insomnia, initial</u> Difficulty in falling asleep
5	0-2	<u>Insomnia, middle</u> Patient restless and disturbed during the night Waking during the night
6	0-2	<u>Insomnia, delayed</u> Waking in early hours of the morning and unable to fall asleep again
7	0-4	<u>Work and Interests</u> Feelings of incapacity Listlessness, indecision and vacillation

A. HAMILTON RATING SCALE OF DEPRESSION contd.

Item No.	Range of Scores	Symptom
8	0-4	<u>Work and Interests</u> contd. Loss of interest in hobbies Decreased social activities Productivity decreased Unable to work Stopped working because of present illness only 4 (Absence from work after treatment or recovery may rate a lower score.)
		<u>Retardation</u> Slowness of thought, speech, and activity Apathy Stupor Slight retardation at interview... 1 Obvious retardation at interview.. 2 Interview difficult..... 3 Complete stupor..... 4
9	0-2	<u>Agitation</u> Restlessness associated with anxiety
10	0-4	<u>Anxiety, psychic</u> Tension and irritability Worrying about minor matters Apprehensive attitude Fears
11	0	<u>Anxiety, somatic</u> Gastrointestinal, wind, indigestion Cardiovascular, palpitations, headaches Respiratory, genito-urinary, etc.
12	0-2	<u>Somatic Symptoms, Gastrointestinal</u> Loss of appetite Heavy feelings in abdomen Constipation

A. HAMILTON RATING SCALE OF DEPRESSION contd.

Item No.	Range of Scores	Symptom
13	0-2	<u>Somatic Symptoms, General</u> Heaviness in limbs, back, or head Diffuse backache Loss of energy and fatiguability
14	0-2	<u>Genital Symptoms</u> Loss of libido Menstrual disturbances
15	0-4	<u>Hypochondriasis</u> Self-absorption (bodily) Preoccupation with health Querulous attitude Hypochondriacal delusions
16	0-2	<u>Loss of Weight</u>
17	2-0	<u>Insight</u> Loss of insight..... 2 Partial or doubtful loss.. 1 No loss..... 0 (Insight must be interpreted in terms of patient's understanding and background)
18	0-2	<u>Diurnal Variation</u> Symptoms worse in morning or evening Note which it is
19	0-4	<u>Depersonalization and Derealization</u> Feelings of unreality } Nihilistic ideas } Specify
20	0-4	<u>Paranoid Symptoms</u> Suspicious Ideas of reference Delusions of reference and persecution Hallucinations, persecutory) Not with a depressive quality
21	0-2	<u>Obsessional Symptoms</u> Obsessive thoughts and compulsions, against which the patient struggles

B. HAMILTON RATING SCALE OF ANXIETY

All items are rated from 0-4 in severity.

Item No.	Symptom	Item No.	Symptom
1	<u>Anxious mood</u> Worries Anticipation of the worst Apprehension (fearful anticipation) Irritability	6	<u>Depressed mood</u> Loss of interest Lack of pleasure in hobbies Depression Early waking Diurnal swing
2	<u>Tension</u> Feelings of tension Fatiguability Inability to relax Startle response Moved to tears easily Trembling Feelings of restlessness	7	<u>General somatic</u> (muscular and sensory) Muscular pains and aches Muscular stiffness Muscular twitchings Clonic jerks Grinding of teeth Unsteady voice Tinnitus Blurring of vision Hot and cold flushes Feelings of weakness Pricking sensations
3	<u>Fears</u> Of Dark Strangers Being left alone Large animals, etc. Traffic Crowds	8	<u>Cardiovascular symptoms</u> Tachycardia Palpitations Pain in chest Throbbing of vessels Fainting feelings Missing beat
4	<u>Insomnia</u> Difficulty in falling asleep Broken sleep Unsatisfying sleep and fatigue on waking Dreams Nightmares Night terrors	9	<u>Respiratory symptoms</u> Pressure or constriction in chest Choking feelings Sighings Dyspnoea
5	<u>Intellectual (cognitive)</u> Difficulty in concentration Poor memory		

B. HAMILTON RATING SCALE OF ANXIETY contd.

Item No.	Symptom	Item No.	Symptom
10	<u>Gastro-intestinal symptoms</u> Difficulty in swallowing Wind Dyspepsia: pain before and after meals burning sensations fullness waterbrash nausea vomiting sinking feelings 'Working' in abdomen Borborygmi Looseness of bowels Loss of weight Constipation	13	<u>Behaviour at interview</u> Tense, not relaxed Fidgetting: hands, picking fingers, clenching, ties, handkerchief Restlessness: pacing Tremor of hands Furrowed brow Strained face Increased muscular tone Sighing respirations Facial pallor Swallowing Belching Tremor Dilated pupils Sweating Twitching
11	<u>Genito-urinary symptoms</u> Frequency of micturition Urgency of micturition Amenorrhea Menorrhagia Development of frigidity Ejaculatio praecox Loss of erection Impotence		
12	<u>Autonomic symptoms</u> Dry mouth Flushing Pallor Tendency to sweat Giddiness Tension headache Raising of hair		

APPENDIX II

CONVERSION FACTORS S.I. TO TRADITIONAL UNITS

Tryptophan:	$1 \mu\text{mol/l} \approx 0.204 \mu\text{g/ml}$
Oestrone:	$1 \text{ pmol/l} \approx 0.0270 \text{ ng/100 ml}$
Oestradiol:	$1 \text{ pmol/l} \approx 0.0272 \text{ ng/100 ml}$
Prolactin	$1 \text{ IU/l} \approx 0.050 \text{ ng/ml}$

APPENDIX III REPRINTS OF PUBLISHED PAPERS

Double-Blind Study on the effect of Oestrogen on Sleep, Anxiety and Depression in Perimenopausal Women: Preliminary Results

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I report preliminary results of a double-blind, controlled study of the effect of oestrogen therapy on the symptoms of insomnia, anxiety, depression and hot flushes in perimenopausal women.

Surveys carried out by Ballinger (1975), Jazman *et al.* (1969) and Thompson *et al.* (1973) have shown that these symptoms are very common about the time of the menopause. Hot flushes are believed to be due to oestrogen deficiency, but the cause of the other symptoms remains obscure. Feinberg *et al.* (1967) found that older people have more broken sleep, which may account for the complaint of sleeplessness. Possible causes of the psychological symptoms associated with the menopause include the social changes of middle age, fear of ageing and of loss of attractiveness, and oestrogen deficiency.

McKinlay & McKinlay (1973) reviewed studies of the effect of oestrogen therapy on menopausal symptoms but could draw no firm conclusions because of differences in age groups studied, and difficulties in assessment of change. There is no agreement on which symptoms can be included in the menopausal syndrome, or as to when it occurs. A further problem is the pronounced placebo effect, which may last for several months (Coope *et al.* 1975, Donovan 1951).

Method

Sixteen women, aged 45-55, with at least three months' amenorrhoea, and symptoms of hot flushes, anxiety, depression and insomnia were studied. The aim is to complete the study on 40 suitable patients who were not receiving any medication were referred by local general practitioners. The study lasted for fourteen weeks. Patients were paired, one serving as a control for the effects of time, placebo, and attention from the researchers. Both patients received a placebo

for the first six weeks of the study, and one received piperazine oestrone sulphate (Harmogen) in a dose of 3 mg per day for the remaining eight weeks, while the control patient remained on placebo. All patients were told they might be given an inert pill.

Patients attended the sleep laboratory one night per week for electrophysiological recording of sleep. The first two nights were for adaptation purposes only, the next four for gathering baseline data and the next four were during the transition period, while oestrogen intake became established; the remaining four were in the final month. The sleep records were scored according to international criteria (Rechtschaffen & Kales 1968). Patients rated their sleep quality, mood and anxiety daily using 100 mm visual analogue scales, and also noted the number of hot flushes they had each day. Observer rating scales of anxiety (Hamilton 1959) and depression (Hamilton 1960) were completed at the beginning and end of the baseline placebo period, at the end of the transition period, and the end of the final month.

Patients also attended one extra night in the baseline period and one in the final month for blood studies. On these nights electrophysiological recording of sleep was carried out; in addition, blood samples were taken at 20 minute intervals through an indwelling cannula (Ogunremi *et al.* 1973). Blood was centrifuged immediately and the plasma stored at -20°C. Each sample was assayed for oestrone, oestradiol, free and total plasma tryptophan, and prolactin.

Results

Sixteen people so far have completed the trial. Seven others dropped out in the first week, and two more left because of taking tranquillizers.

The placebo group ($n=8$) had a mean age of 48.8, and the oestrone group ($n=8$) had a mean age of 50.1. In each group there were 3 women with amenorrhoea lasting between three and twelve months, 3 with 2–5 years' amenorrhoea, and 2 who were more than five years post-menopausal.

Both groups showed a decrease in the numbers of hot flushes, but there was no significant difference between the two groups. At the present preliminary stage, subjective measures of mood, anxiety and sleep quality have failed to show a significant difference between the two groups, and only objective measures of sleep have shown a significant difference. No significant difference between the baseline placebo period and transitional period was found. Comparing, however, the baseline period and the final month, there was a mean increase in sleep duration of 24.1 ± 7.7 min in the oestrone group. The placebo group had a mean increase in sleep duration of 3.7 ± 5.2 min. Using a Student's *t* test the difference between the two groups is significant ($t=2.2$, $P<0.04$). An *I*-tailed test was used, since this change had been predicted.

When comparing the brokenness of sleep in the baseline period and the final month, intervening wakefulness (the amount of time spent awake between first going to sleep and the time when a total of 6 hours' sleep had been accumulated) was decreased by 9.6 ± 4.4 min in the oestrone group. The placebo group showed an increase of 0.5 ± 3.2 min in intervening wakefulness. The difference between the two groups is just short of statistical significance ($t=1.86$, $P=0.052$).

The analysis of the blood samples is not yet complete. Three nights' samples of different subjects have been assayed for oestrogens and free and total plasma tryptophan. A significant positive correlation between total plasma oestrogen concentration and concentration of free plasma tryptophan, and also between total oestrogen concentration and percentage free plasma tryptophan, has been found in all cases (to be published elsewhere).

Discussion

These results do not so far show that oestrogen is significantly better than placebo in relieving depression, anxiety and hot flushes in perimenopausal women. This may be due to the small numbers studied or to the pronounced placebo effect on menopausal symptoms (Coope *et al.* 1975, Donovan 1951).

We have shown that oestrogen produces a significant increase in sleep duration, and a decrease in intervening wakefulness in the first 6 hours of sleep that borders on statistical significance. We have also found a significant positive

correlation between plasma oestrogen concentration and free plasma tryptophan levels. The level of free plasma tryptophan has been shown to affect the rate of synthesis and turnover of serotonin in the brain (Fernstrom & Wurtman 1971, Gessa *et al.* 1972, Knott & Curzon 1972). There is evidence from animal studies (Jouvet 1969) that cerebral serotonin is involved in the maintenance of sleep. It is possible that insomnia in menopausal women is due to falling oestrogen levels producing a fall in free plasma tryptophan, which then influences cerebral serotonin metabolism. The increase in sleep duration with therapy may be due to exogenous oestrogen causing an increase in free plasma tryptophan.

Coppen *et al.* (1972) reported that free plasma tryptophan levels were low in depressed women, but other workers (Niskanen *et al.* 1976, Peet *et al.* 1976) have produced conflicting results. Aylward (1973) found that free plasma tryptophan concentrations were low in depressed menopausal women, but that oestrogen therapy both relieves the depression and increases the free plasma tryptophan levels. The possibility that free plasma tryptophan concentration falls in parallel with oestrogen levels at the time of the menopause, and that this causes the depression which is so common at this time, requires further investigation.

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Effect of oestrogen on the sleep, mood, and anxiety of menopausal women

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Summary

A double-blind controlled study of the effect of piperazine oestrone sulphate on sleep, depression, anxiety, and hot flushes was performed in 34 perimenopausal women. Half of the patients were given six weeks' placebo followed by eight weeks' oestrogen, and half remained on placebo throughout. Sleep was recorded electrophysiologically every week, and mood and anxiety were rated daily by means of visual analogue scales. Hot flushes were counted daily. Observer rating scales of anxiety and depression were completed at intervals.

During the first month of active treatment the amount of intervening wakefulness in the first six hours of sleep decreased significantly more in the oestrone group than in those on placebo. Between the baseline period and the second treatment month the oestrone group showed a significantly greater decrease in the total amount of intervening wakefulness and in the frequency of awakenings. Their total amount of rapid eye movement sleep increased. Mood and anxiety improved and the number of hot flushes decreased to a similar degree in both groups.

Although oestrogen did reduce the number of episodes of wakefulness in perimenopausal women complaining of insomnia, its effects on their psychological symptoms were little different to those of placebo.

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Introduction

The perimenopausal period has long been considered to be a time of increased morbidity, and various epidemiological surveys¹⁻³ have shown that complaints of hot flushes, insomnia, depression, and anxiety are especially common at this time. The symptoms may be due to hormonal changes, but it is also possible that the psychological symptoms might be due to fear of aging or to the social changes of middle age. Jaszman¹ and Ballinger¹ have inferred that insomnia is due to hormonal changes, since their surveys have shown that the incidence of the complaint rises as oestrogen levels fall in the perimenopausal period. Other possible causes are aging, anxiety, and depression, all of which are associated with sleep disturbance.⁵⁻⁷

Hormone replacement therapy has been used to treat menopausal symptoms since 1896 but remains controversial. McKinlay and McKinlay⁸ reviewed the many studies of hormone replacement therapy but found that results were conflicting and that studies lacked consistency in defining the menopause, the symptoms associated with it, and the age group to be studied.

We therefore carried out a double-blind controlled study of the effect of oestrogen therapy on sleep, mood, anxiety, and hot flushes in perimenopausal women.

Patients and methods

Patients were referred by local general practitioners. All were aged 45-55 and had had amenorrhoea for at least three months and symptoms of insomnia, depression, anxiety, and hot flushes. They received no other medication, had no contraindications to oestrogen therapy, and were asked to abstain from alcohol for the duration of the study.

Each patient was studied for 14 weeks, and throughout this time they attended the sleep laboratory in pairs on one night each week for electrophysiological recording of sleep. In the first six weeks all patients received a placebo. In the remaining eight weeks one of each pair received piperazine oestrone sulphate in a dose of 1.5 mg twice daily while the other remained on placebo. All patients were warned that the pills they received might be blanks.

The first two nights spent in the sleep laboratory were for adaptation purposes only, and the next four were for baseline recordings. The subsequent four nights were in the first treatment month and the final four in the second treatment month. Ultimately the sleep records were scored blind according to standard criteria.⁹

Each day throughout the study patients rated their mood and anxiety, using 100-mm visual analogue scales, and they noted the number of hot flushes they experienced. Hamilton observer rating scales of anxiety¹⁰ and depression¹¹ were completed at the beginning and end of the baseline placebo period, at the end of the first treatment

month, and at the end of the second treatment month.

Statistics—Intragroup changes in the different periods of the experiment were compared by *t* tests for paired observations. The changes between the baseline period and first treatment month and between the baseline and second treatment month were also examined for each group, and the magnitude of change in the two groups was then compared using Student's *t* test. A one-tailed test was used for intervening wakefulness and frequency of arousals, which we had predicted would decrease with oestrogen treatment, and a two-tailed test in all other cases.

Results

Thirty-four patients completed the study. Eight others had started but failed to complete the study, seven dropping out in the first week, and one in the eighth week because of urinary tract infection. The mean age was 49.7 years in the oestrogen group ($n=17$) and 48.5 years in the placebo group ($n=17$). The two groups were comparable in terms of menstrual age.

SLEEP DURATION

The duration of sleep increased in both groups. In the oestrogen group mean sleep duration (\pm SE) increased from a baseline value of 423.2 ± 8.2 minutes to 442.2 ± 7.7 minutes in the first treatment month ($t=3.305$; $P<0.01$) and rose to 446.5 ± 7.2 minutes in the second treatment month ($t=2.939$; $P<0.01$). In the placebo group the increase from the baseline duration of 418.2 ± 7.2 minutes to 424.3 ± 8.2 minutes in the first treatment month was not significant, but the increase from the baseline value to 429.4 ± 7.2 minutes in the second treatment month was significant ($t=2.735$; $P<0.02$). The difference between the two groups was not significant.

INTERVENING WAKEFULNESS

A measure of the brokenness of sleep is provided by the amount of time awake that intervenes between periods of sleep. Comparing the baseline period and the first treatment month, the oestrone group showed a decrease in the amount of intervening wakefulness during the whole of sleep of 14.4 ± 5.1 minutes, and the placebo group showed a decrease of 4.7 ± 4.5 minutes. The difference between the two groups was just short of significance ($t=1.454$). In the second treatment month the oestrone group had 15.8 ± 5.8 minutes less intervening wakefulness than in the baseline period and the placebo group 2.1 ± 2.2 minutes less. The difference between the two groups was significant ($t=2.176$; $P<0.025$).

The oestrone-treated group also woke less often. In the second treatment month they showed a decrease in the number of arousals from sleep to wakefulness of 0.9 ± 0.4 compared with the baseline period, whereas the placebo group showed a small mean increase of 0.1 ± 0.4 . The difference between the two groups was significant ($t = 1.717$; $P < 0.05$).

The results were also analysed in terms of the first six hours of accumulated sleep to keep the sleep duration constant among subjects and nights. The mean cumulative intervening wakefulness in the first six hours of sleep in oestrone and placebo groups is shown in fig 1. The mean value during the baseline period was higher in those who later received oestrone, but not significantly so ($t = 1.140$; NS). Between the baseline period and first treatment month the oestrone group showed a decrease in intervening wakefulness of 17.2 ± 6.6 minutes and the placebo group a decrease of 2.6 ± 4.6 minutes ($t = 1.816$; $P < 0.05$). When the baseline value was compared with that in the second month of treatment the oestrone group showed a

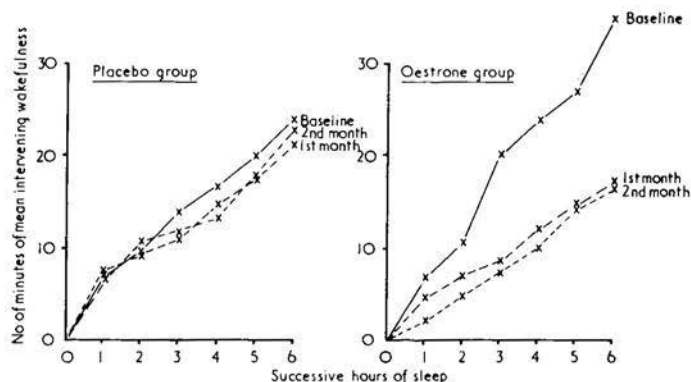


FIG 1—Mean cumulative wakefulness intervening during accumulation of first six hours of sleep in oestrone and placebo groups in baseline period, first treatment month, and second treatment month.

decrease of 18.0 ± 7.3 minutes and the placebo group a decrease of only 1.0 ± 2.4 minutes, the difference between the two groups again being significant ($t = 2.205$; $P < 0.025$).

The number of arousals to wakefulness in the first six hours of sleep in the two groups is shown in fig 2. The oestrone group showed a decrease in the number of awakenings of 1.1 ± 0.5 between the baseline and second treatment months, while the placebo group showed an increase of 0.2 ± 0.3 . The difference between the two groups was significant ($t = 2.260$; $P < 0.025$).

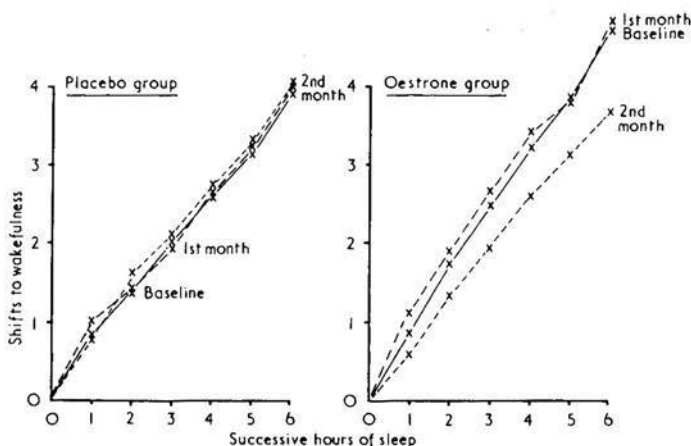


FIG 2—Cumulative mean number of awakenings in first six hours of sleep in oestrone and placebo groups in baseline period, first treatment month, and second treatment month.

SLEEP STAGES

The total amount of rapid eye movement (REM) sleep in the oestrone group increased throughout the study. Between the baseline month and first treatment month the difference between the groups was not significant, but between the baseline and second treatment months the oestrone group showed an increase in REM sleep of 13.3 ± 4.7 minutes and the placebo group of 2.3 ± 2.0 minutes: the difference between the groups was significant ($t = 2.184$; $P < 0.05$). There was no increase in REM sleep in the first six hours of sleep in either group.

No significant changes in stage 1, stage 2, or slow-wave sleep were observed.

MOOD

Both oestrone and placebo groups showed an improvement in mood throughout the study, as shown by Hamilton rating scales and visual analogue scales. The mean Hamilton depression score of the oestrone group was 16.3 ± 1.9 at the start of the study, 7.9 ± 1.2 at the end of the baseline period, 7.3 ± 1.3 at the end of the first treatment month, and

5.9 ± 1.8 at the end of the second treatment month. Over the same period the scores of the placebo group fell from 18.2 ± 2.0 to 10.1 ± 1.5 , to 6.2 ± 1.3 , and finally to 4.5 ± 0.7 .

In both groups the difference in values between the start and end of the baseline period was significant (oestrone group: $t = 4.465$, $P < 0.001$; placebo group: $t = 6.125$; $P < 0.001$). In the placebo group there was a significant decrease from the end of the baseline period to the end of the first treatment month ($t = 2.810$; $P < 0.02$) and to the end of the second treatment month ($t = 3.301$; $P < 0.01$), but in the oestrone group these changes did not reach significance ($t = 0.997$ and 1.552). There were no significant differences between the two groups.

ANXIETY

Both oestrone and placebo groups showed a steady improvement in anxiety as measured by Hamilton anxiety rating scales and visual analogue scales throughout the study. The Hamilton anxiety score of the oestrone group fell from 17.2 ± 1.8 at the start of the study to 9.7 ± 1.3 at the end of the baseline period, 7.7 ± 1.2 at the end of the first treatment month, and 5.6 ± 1.4 at the end of the second treatment month. The scores of the placebo group fell from 20.1 ± 2.1 to 11.4 ± 1.3 , to 6.5 ± 1.1 , and to 5.4 ± 0.7 at the end of the study.

In both groups the difference in values between the start of the study and the end of the baseline period was significant (oestrone group: $t = 5.455$, $P < 0.001$; placebo group: $t = 5.605$, $P < 0.001$). The decrease from the end of the baseline period to the end of the first treatment month was significant for the placebo group ($t = 4.363$; $P < 0.001$) but not for the oestrone group ($t = 1.748$), and the decrease from the end of the baseline period to the end of the study was significant in both groups (oestrone group: $t = 3.422$, $P < 0.01$; placebo group: $t = 4.348$, $P < 0.001$). There were no significant differences between the two groups.

HOT FLUSHES

The mean hot flush count of both groups fell steadily throughout the study, from a mean of 14.4 ± 4.4 per week at the outset to 8.5 ± 3.3 in the 14th week in the placebo group and from 13.3 ± 3.6 to 5.9 ± 2.2 in the case of the oestrone group. There were no significant differences between the two groups.

Discussion

We have shown that oestrogen treatment diminishes the number and duration of episodes of wakefulness that interrupt sleep in perimenopausal women complaining of insomnia. The patients treated with oestrogen also showed an increase in the duration of sleep, but this did not reach significance when oestrone and placebo groups were compared. The increase in

REM sleep shown by the oestrogen group in the second treatment month was probably due to the increase in sleep duration, since no changes in REM sleep were found in the first six hours of sleep, and it is known that REM periods become more frequent and prolonged towards the end of the night.

We have previously reported a highly positive correlation between nocturnal plasma oestrogen and free plasma tryptophan concentrations in perimenopausal women,¹² and Aylward¹³ has reported that oestrogen treatment increases free plasma tryptophan concentrations in perimenopausal women. Free plasma tryptophan is the precursor of the cerebral neurotransmitter serotonin, and Jouvet¹⁴ has proposed that serotonin depletion by pharmacological means leads to insomnia. Falling oestrogen levels at the time of the menopause may lead to a fall in free plasma tryptophan concentrations, which is reversed by oestrogen therapy, and the effect of oestrogen in sleep may be mediated through changes in plasma tryptophan influencing cerebral serotonin metabolism.

We found that depression, anxiety, and hot flushes in these perimenopausal women responded strongly to placebo. Donovan¹⁵ reported that in 95% of cases menopausal symptoms could be relieved by history-taking alone, while an injection of saline relieved symptoms in the remainder. Pratt and Thomas¹⁶ also observed a pronounced placebo effect in their blind controlled study and found no significant difference between oestrogen and placebo in relieving either physical or psychological symptoms.

Subjective rating methods for measuring such factors as mood are less precise and less suitable for studying small groups than the objective, electrophysiological measures. This may have contributed to our failure to find that oestrogen was significantly more effective than placebo in relieving depression and anxiety in menopausal women. Our findings contrasted with those of Aylward,¹³ who found in a double-blind study using the same dose and type of oestrogen that we used that oestrogen did relieve depression. His patients, however, had undergone oophorectomy and may therefore have differed from women who have experienced a physiological menopause, since the postmenopausal ovary secretes androgenic hormones.^{17,18} Utian¹⁹ and George *et al.*²⁰ also carried out controlled studies of the effect of conjugated equine oestrogens on the psychological symptoms of women who had undergone oophorectomy. Utian reported that oestrogen had a mental tonic effect, but George, who used a smaller dose of oestrogen, found that oestrogen was not significantly more effective than placebo in relieving psychological symptoms and suggested that the mental tonic effect might be dose-related.

We found a marked placebo effect on hot flushes, similar to that described by Coope *et al*²¹ and Pratt and Thomas,¹⁶ and it was not possible to predict on the basis of changes in hot flush count or severity which patients were receiving oestrogen therapy.

In conclusion, whereas we found only placebo effects on depression, anxiety, and hot flushes, oestrogen treatment produced an objective decrease in the brokenness of sleep in perimenopausal women complaining of insomnia.

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Hormones and sleep

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Summary

The secretion of several hormones increases during the night and this is sometimes due to a circadian rhythm (e.g. corticosteroids) and sometimes contingent on sleep (e.g. growth hormone, prolactin). It has been postulated that sleep is a time that facilitates growth and restorative processes. Growth hormone secretion during sleep is increased when greater restorative processes may be presumed, e.g. after exercise or sleep deprivation. Luteinizing hormone and testosterone are sleep-dependent at the time of puberty. A study is currently being carried out to investigate the relationship between sleep and oestrogen at the menopause. A double-blind, controlled study of the effect of piperazine oestrone sulphate (1.5 mg b.d.) on sleep, mood, anxiety levels and hot flushes in menopausal women is described. Preliminary results on 16 subjects show a significant increase in sleep duration in patients on oestrogen ($p < 0.04$) with a decrease in intervening wakefulness on the border of significance ($p < 0.06$). Blood studies during sleep show a highly significant positive correlation between total plasma oestrogen concentration (unconjugated oestrone and oestradiol) and both free plasma tryptophan concentration and % free plasma tryptophan. This suggests a means by which plasma oestrogen may influence cerebral serotonin metabolism, and hence mood, in menopausal women.

Key words: Piperazine oestrone sulphate – sleep – menopause

Introduction

Bodily functions change during sleep and since the central nervous system and the endocrine system always co-operate in the regulation of bodily function, it is not surprising that sleep has many relationships with the endocrines. The relationships between sleep and hormones are studied by sampling blood during sleep. Electrodes attached to the head are used to record brain electrical rhythms, muscle tone and eye movements. A catheter is inserted into the forearm vein before the patient or volunteer goes to bed and an extension to the catheter passes through the bedroom wall and allows blood samples to be taken through the night without disturbing the sleeper.

The levels of many hormones rise at night. In some cases the 24-hour rise and fall is a manifestation of a circadian rhythm and is not dependent on sleep. Corticosteroids, for example, rise towards the end of the night, whether the individual has slept or been kept awake. However, in 1968 Japanese workers showed that there was

increased secretion of human growth hormone during the night^{14,28} and this rise is dependent on sleep.²⁵ Sleep-dependent secretion does not take place at the usual time if the individual stays awake but instead is delayed until he has gone to sleep.

Growth hormone increases the rate of synthesis of protein and enhances the burning of fat as fuel, so sparing amino acids. The sleep-dependent rise in growth hormone lends support to the view that sleep enhances growth and restorative processes.¹ Re-growth of skin occurs especially during the sleep period in humans¹⁰ and the mitotic index has been reported to rise during the sleep period in a wide variety of the ectodermal tissues of rodents which sleep during the day and are awake at night. In other ectodermal tissues in which mitoses do not occur, such as the brain, there is greatly increased protein synthesis during sleep.²¹ The same is true of mesodermal tissues such as muscle²² and cartilage.²⁷ Endodermal tissues also show more mitoses during the sleep period, gastric epithelium being an example.⁶

In man, the metabolic conditions peculiar to sleep mean that growth hormone is more effective in promoting protein synthesis if given at the beginning of sleep. Rudman *et al.*²³ showed that nitrogen retention, an index of protein synthesis, was significantly greater when growth hormone was injected just prior to sleep than when it was injected in the morning. The secretion of growth hormone is greater under conditions when greater restoration is needed. Thus, monkeys deprived of sleep for 3 days and nights secrete significantly more growth hormone when they are allowed to sleep.¹⁵ At Edinburgh, it was demonstrated that heavy exercise during the day significantly increases the secretion of nocturnal growth hormone.² Other hormones have since been found to be sleep-dependent for their main secretion of the 24 hours. The large nocturnal secretion of prolactin is sleep-dependent²⁴ and children in early puberty secrete more luteinizing hormone and more testosterone during their sleep.⁴

The brain electrical rhythms of sleep can be categorized into stages, and it has been observed that the stage in which growth hormone is secreted – Stage 4 or slow wave sleep – is enhanced under conditions when one could expect a greater need for restorative processes. Whereas Stage 4 sleep is absent in hypothyroid middle-aged patients, a group of hyperthyroid patients studied at Edinburgh had abnormally large amounts of Stage 4 sleep.⁸ A further example of the interaction between hormone status by day and sleep by night is provided by the findings of Johns *et al.*,¹⁷ who studied the day-to-day fluctuations in thyroxine secretion and found that after days when normal men had higher thyroxine secretion they had more Stage 4 sleep at night.

Recent work at Edinburgh has been designed to see whether there are other connections between hormone status, sleep and the menopause. The menopause is associated with a decline in oestrogen production, and also with a high incidence of insomnia. Jaszmann *et al.*¹⁶ surveyed 2933 women aged 40 to 60 years, and found that 20% of pre-menopausal women complained of insomnia, rising to 40% 2 to 5 years after the menopause, and falling to 30% 10 years after the menopause. Sherman *et al.*²⁶ found that oestradiol levels fall before the menopause, while Chakravarti *et al.*⁵ found that oestrogen levels fell to 20% of normal levels within 1 year of the menopause, remaining low for 10 years but rising thereafter. This suggests a relationship between oestrogen levels and insomnia. However, other causes of insomnia have

been suggested. Thompson *et al.*²⁹ suggested that insomnia at the menopause may be due to night sweats. Williams *et al.*³¹ showed that there is an increase in the frequency and duration of episodes of wakefulness in the sleep of older people, and this may contribute to the insomnia of post-menopausal women. The insomnia may also be due to depression or anxiety, which are common symptoms at this stage in life.

Oestrogens and sleep at the menopause

To determine the relationship between oestrogens and sleep at the menopause, we are currently conducting a double-blind controlled trial of the effect of oestrogen therapy on the sleep, mood and anxiety levels of menopausal women. Local general practitioners refer suitable patients, who must be aged 45 to 55 years old, with at least 3-months' amenorrhoea and symptoms of insomnia, hot flushes, anxiety and depression. They should not be on any other medication, and must abstain from alcohol throughout the study. Patients with a history of jaundice, malignancy and thrombo-embolic phenomena are excluded. A total of 40 patients will be studied.

The study lasts 14 weeks for each patient. The first 6 weeks are termed the baseline period, when all patients are on placebo. The next 4 weeks are termed the transition period, and the remaining 4 the final month. Patients attend the sleep laboratory in pairs. For the first 6 weeks both take a placebo, but during the transition period and final month, one of the pair receives piperazine oestrone sulphate in a dose of 1.5 mg b.d. The other patient remains on placebo throughout, to control for the effect of time, placebo, and the attention of the researchers. All are warned that the pills may be blanks.

Patients attend the sleep laboratory 1 night per week for electrophysiological recording of sleep. The first 2 nights are for adaptation purposes only, the next 4 are in the baseline period, the next 4 in the transition period, and the remaining 4 in the final month. The sleep records are scored according to international criteria.²⁰ Patients rate their sleep quality, mood and anxiety daily using 100 mm visual analogue scales, and also note the number of hot flushes they have had each day. Observer rating scales of anxiety¹² and depression¹³ are completed at the beginning and end of the baseline placebo period, at the end of the transition period, and the end of the final month.

The study has not yet been completed. The results of 16 patients have so far been analysed. The oestrone group ($n=8$) had a mean age of 50.1 years, the placebo group ($n=8$) had a mean age of 48.8 years. In each group there were 3 patients with amenorrhoea lasting between 3 and 12 months, 3 patients with 2 to 5 years of amenorrhoea, and 2 patients who were more than 5 years post-menopausal.

Both groups showed a steady improvement in sleep quality, mood and anxiety levels, and a fall in the number of hot flushes. At this early stage there is no significant difference between the two groups in respect of such symptoms. At present, only objective measures of sleep have shown a significant difference between the two groups.

No significant difference between the baseline period and the transition period was found. However, comparing the baseline period and the final month, the oestrone group showed a mean increase in sleep duration of 24.1 ± 7.7 min. The placebo group had a mean increase of 3.7 ± 5.2 min. Using a Student's t-test the difference between the two groups is significant ($t=2.2$, $p<0.04$). A one-tailed t-test was used since this difference had been predicted.

A measure of the brokenness of sleep, or intervening wakefulness, is the amount of time spent awake between going to sleep and accumulating 6 hours of sleep. The oestrone group showed a mean decrease of intervening wakefulness of 9.6 ± 4.4 min between the baseline period and the final month. The placebo group showed a mean increase of 0.5 ± 3.2 min in intervening wakefulness in the same period. The difference between the two borders on significance, $t=1.86$, $p=0.052$.

Patients may also attend the sleep laboratory for blood studies on 2 extra nights, 1 in the baseline period and 1 in the final month. Sleep is recorded as usual on those nights, and blood samples are taken at 20 min intervals throughout the night. Blood samples are centrifuged immediately and plasma stored at -20°C . Each sample is assayed for oestrone, oestradiol, free and total plasma tryptophan, prolactin and magnesium. Three night samples of different subjects on placebo have been analyzed so far. A significant positive correlation between total plasma oestrogen concentration (unconjugated oestrone+oestradiol) and free plasma tryptophan concentration, and also between total oestrogen concentration and percentage free plasma tryptophan has been found.³⁰

The relationship between plasma oestrogen concentration and free plasma tryptophan provides a link between oestrogens in plasma and cerebral serotonin metabolism. The concentration of free plasma tryptophan has been shown to affect the rate of synthesis and turnover of serotonin in the brain.^{9,11,19} Jouvet¹⁸ has proposed that cerebral serotonin is concerned in the maintenance of sleep and, if so, falling oestrogen levels at the menopause might produce insomnia by decreasing free plasma tryptophan concentration and thus influencing brain serotonin metabolism. The increase in sleep duration, and decrease in intervening wakefulness, could then be due to oestrogen therapy reversing this fall in free plasma tryptophan levels. Coppen *et al.*⁷ have reported a fall in free plasma tryptophan in depressed women and Aylward³ has reported that oestrogen therapy both increased free plasma tryptophan levels and relieved depression in menopausal women. The possibility that falling levels may cause depression by producing a parallel fall in free plasma tryptophan levels requires further investigation.

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Discussion

Dr. S. Contractor (*Charing Cross Hospital, London*): There is another possible explanation, isn't there, of the mechanism of action of oestrogen on sleep and that is that oestradiol is known to act on the tryptophan – xanthurenic acid pathway and, therefore, it may be removing the tryptophan available for your 5HT pathway.

Dr. J. Thomson: That is a possible explanation, but it really needs further investigation.

Dr. M. Aylward (*Glamorgan, S Wales*): May I make a comment on the last suggestion. In fact, oestradiol or oestrone administered to menopausal patients do not increase the excretion of tryptophan metabolites in urine. It is unlikely, therefore, that the data quoted by Dr. Thomson could be explained by induction of hepatic tryptophan metabolizing enzymes by oestrogens.

RELATIONSHIP BETWEEN NOCTURNAL PLASMA OESTROGEN CONCENTRATION AND FREE PLASMA TRYPTOPHAN IN PERIMENOPAUSAL WOMEN

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A study of the relationship between nocturnal endogenous plasma oestrogen and free plasma tryptophan levels in perimenopausal women is reported. The study was approved by the Royal Edinburgh Hospital Ethics Committee, and all subjects gave informed consent.

The three subjects in the study had symptoms associated with the climacterium, including hot flushes, insomnia, and depression. Case 1 was 5 years post-menopausal, Case 2 had 6 months amenorrhoea, and Case 3 had only 6 months amenorrhoea.

Blood was sampled during sleep from 22.30 to 07.00 h at 20 min intervals by means of an indwelling catheter as described by Ogunremi, Adamson, Brezinova, Hunter, MacLean, Oswald & Percy-Robb (1973). It was centrifuged immediately and the plasma deep frozen.

Total plasma tryptophan was measured by the method of Wapnir & Stevenson (1969). Plasma was centrifuged in Centriflo membrane cones (Amicon Ltd) for 30 min at 1000 *g* and free plasma tryptophan assayed in the ultrafiltrate as described by Wapnir & Stevenson (1969) and Denckla & Dewey (1967).

Oestrogens were extracted from plasma with diethyl ether and separated by LH-20 Sephadex column chromatography. Oestrone and oestradiol concentrations were then measured by radioimmunoassay using standard antisera (New England Nuclear) prepared in sheep against oestradiol-17 β -succinyl-albumin. This has 50% cross-reactivity with oestrone, but since the oestrogens were separated before assay, each oestrogen could be measured against this same antiserum, using appropriate standards.

Total plasma oestrogen (unconjugated oestrone + oestradiol) concentration fluctuated during the night without relation to changes in total plasma tryptophan levels. There was, however, a significant positive correlation between total plasma oestrogen concentration and the concentration of free plasma tryptophan. The correlations between total plasma oestrogen and concentration of free plasma tryptophan were: Case 1, $r=0.875$, $P<0.001$; Case 2, $r=0.867$, $P<0.001$; Case 3, $r=0.483$, $P<0.005$.

The correlations between total plasma oestrogen concentration and % free plasma tryptophan were higher (see Fig. 1): Case 1, $r=0.997$, $P<0.001$; Case 2, $r=0.995$, $P<0.001$; Case 3, $r=0.810$, $P<0.001$. There was no correlation between free and total plasma tryptophan concentration in Cases 2 and 3, but for Case 1, $r=0.403$, $P<0.05$.

The mean plasma oestrogen levels were: Case 1, 71.2 ng/l; Case 2, 225.9 ng/l; Case 3, 76.7 ng/l. The oestrone : oestradiol ratio in Case 1 was 3.8 : 1, in Case 2 was 2.3 : 1, and in Case 3 was 3.1 : 1. The mean free plasma tryptophan concentrations were: Case 1, 0.90 mg/l (5.6%); Case 2, 1.83 mg/l (12.2%); Case 3, 1.43 mg/l (10.5%).

The correlation, for the three women, between mean plasma oestrogen concentration and mean % free plasma tryptophan was significant ($r=0.9995$; $n=3$, $P<0.05$). The mean total tryptophan concentration in Case 1 was 13.7 mg/l, Case 2 was 14.8 mg/l, and Case 3 was 13.4 mg/l.

We have shown fluctuations in the concentrations of oestrogen and free plasma tryptophan in plasma from perimenopausal women during the night. There was a significant positive correlation between total oestrogen concentration and concentration and % free plasma tryptophan. The majority of tryptophan in plasma is bound to albumin (McNenamy & Oncley,

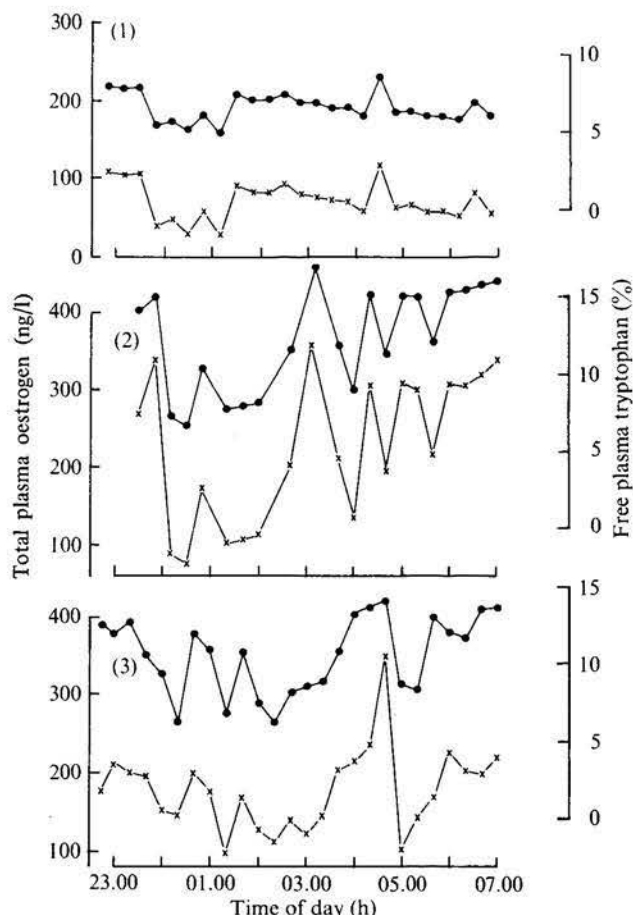


Fig. 1. Relationships between nocturnal plasma oestrogen (unconjugated oestrone and oestradiol) (X) and % free tryptophan (●) in three perimenopausal women.

1958). Oestrogens in plasma bind with high affinity to a specific binding globulin present in low concentrations in plasma, but they can also bind, though with lower affinity, to albumin (Burton & Westphal, 1972). Because of this, it seems likely that the relationship between oestrogen concentration and free plasma tryptophan level is due to a direct action of oestrogen on the tryptophan binding site of albumin. Since the metabolism of brain serotonin depends partly on the concentration of free plasma tryptophan (Fernstrom & Wurtman, 1971; Knott & Curzon, 1972; Gessa & Tagliamonte, 1974) these results suggest a possible means by which oestrogens might influence cerebral serotonin metabolism and perhaps mood in perimenopausal women.

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